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DEPT OF MATHS AND STATISTICS

*Modelling Rates of
Cognitive Decline in
Patients with a
Dementing Illness*

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Submitted for the degree of MPhil

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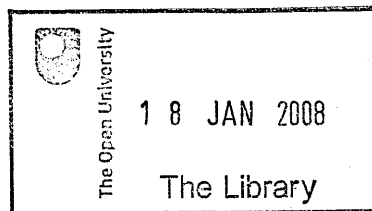
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Contents

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Abstract	vi
1 Introduction	1
2 Background	4
2.1 Dementia	4
2.2 History	4
2.3 Diagnosis	5
2.4 Prevalence	6
2.5 Epidemiology	7
2.5.1 Family history of dementia	7
2.5.2 APOE genotype	8
2.5.3 Down's syndrome	8
2.5.4 Head injury	8
2.5.5 Hormone Replacement Therapy	9
2.5.6 Non-steroidal anti-inflammatory drugs (NSAIDs)	9
2.5.7 Aluminium	9
2.5.8 Smoking	9
2.5.9 Neurocognitive reserve	9
2.5.10 Diet	10
2.6 Measuring the progress of the illness	10
2.7 Comparing rates of decline	11
2.8 Measuring the efficacy of drugs	13
3 The data	14
4 Fitting individual patients	19
5 Determining a time scale	22
5.1 Theory behind the linear model	22
5.1.1 Assumptions of the model	25
6 A fixed-effects Model	30
6.1 Theory behind a fixed-effects model using the binomial or logistic curve	30
6.2 Considering the covariates	33
6.2.1 midpoint age	34
6.2.2 Age at onset	35
6.2.3 Age at episode 1, Correction for episode 1	35
6.2.4 Homocysteine (Hcy)	36
6.2.5 Genotype	36
6.2.6 Diagnosis	36

6.2.7	Heart arrhythmias	36
6.2.8	Drugs	37
6.3	Fitting the model	37
6.4	Effect of a lower initial Camcog	38
7	Random-effects models	42
7.1	Theory behind the random-effects models	42
7.2	Modelling random effects with glmmPQL	43
7.2.1	Results of fitting the data with glmmPQL	43
7.2.2	Fixed effects with glmmPQL	45
7.2.3	Comparison with fixed-effects model	45
7.3	Modelling random effects with nlme	45
8	Comparing the models	52
9	Interpreting the results	55
10	Adjusting Camcog values	59
11	Conclusions	62
A	R output of model refinement	65

List of Figures

1.1	Theoretical picture of the decline	2
2.1	Prevalence of dementia by age	7
2.2	Projection of cases of dementia	8
2.3	Results of trial with Rivastigmine	13
3.1	Some sample individual Camcog scores over time	17
3.2	Age at First Visit	18
3.3	Number of visits per patient	18
4.1	Some sample logistic regression models	20
5.1	Central part of the decline for one patient	23
5.2	Central decline with linear model	25
5.3	Deviance residuals-fitted values for Patient ID 007	26
5.4	QQ plot for linear model	26
5.5	Sample linear models from four patients	28
5.6	Boxplot of Confidence Intervals	29
6.1	Complete Camcog scores over time	31
6.2	Boxplot of Mid-point ages	34
6.3	Boxplot of transformed mid-point ages	35
6.4	Cooks distances showing the influential point	39
6.5	Residuals vs Fitted values for fixed effects model	39
6.6	Diagnostic plots for the final fixed effects model	40
6.7	Comparison of models with differing initial Camcog scores	40
7.1	Residuals vs Fitted values for glmmPQL model	44
7.2	Diagnostics for the final random effects model	44
7.3	Comparison of fixed and random effects models	46
7.4	Theoretical model of 3-parameter nlme	47
7.5	Pairs plot from the nlme model	48
7.6	Plot of fitted values vs residuals for nlme	48
7.7	Diagnostics for nlme model with random effects on all parameters	49
7.8	Predicted decline from nlme at limits of Asym	50
7.9	Predicted decline from nlme at limits of scal	50
7.10	Predicted decline from nlme at limits of xmid	51
8.1	95 percent CI of errors on mid-point ages	53
9.1	Effect of changing the model parameters	56
10.1	Final model and raw Camcog points	60
10.2	Final model and adjusted Camcog points	60

10.3 Final model and adjusted Camcog points	61
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List of Tables

3.1	Demographics of Optima patients with dementia	15
6.1	Summary of midpoint ages	34
6.2	Results of the fixed effects model	38
6.3	Comparison of models with differing initial Camcog scores	41
7.1	Significant covariates from glmmPQL model	45
7.2	Comparison of fixed effects and random effects models	45
7.3	Comparison of nlme models with varying random effects	47
7.4	Parameters calculated by nlme	49
8.1	Parameters and p-values from fixed- and random-effects models	54
9.1	Comparison of change in Camcog for differing covariates	56
9.2	Effect of age on impairment ratio	57
9.3	Interaction of Homocysteine and APOE impairment ratios	58
11.1	Estimates for impairment ratios	63

Abstract

Optima is an Oxford-based longitudinal study of people with dementia, and non-demented elderly. The results of cognitive tests of 123 Optima patients with dementia (age at first visit 44 - 89 years, mean 72.2; 76 females, 47 males; 2 - 21 visits, mean 7.9) are analysed. The test used was the cognitive component of the Cambridge Mental Disorders of the Elderly Examination (Camdex). The rate of decline varies markedly between patients; in their first year a few patients show an increased score; the mean decline is 14 Camcog points, and the maximum 61.

The decline of individual patients is modelled by fitting the test scores with the binomial or logistic variant of the general logistic model (as shown in figure 1.1), generally giving a good fit to the data. A method of centering the individual curves about the midpoint of the cognitive scale is developed, which puts patients on a common time-scale and allows all the data to be incorporated into a single fixed-effects model. This method has the power to look at many possible covariates and identify those which apparently have significant effects.

A random-effects model is then adopted (theoretically more plausible) to carry out a more rigorous analysis which confirms these results. Both models show the rate of decline is strongly affected by:

- Age at Camcog midpoint
- Initial homocysteine level
- APOE genotype
- Anti-cholinesterase drugs

In order to show the relative effects of these covariates the idea of the **decline ratio**, similar to the odds-ratio, is introduced. Its purpose is to quantify the effect of one variable on the progress of the disease, all other things being equal. Younger patients, those with the APOE44 allele and those without the APOE44 allele but with an initially high level of homocysteine, are more likely to have a rapidly progressing illness. Patients who take anticholinesterase drugs in the early stages of their illness are likely to show a slower decline.

Chapter 1

Introduction

Alzheimer's disease is the best-known of a group of degenerative illnesses which affect functioning of the brain, causing a progressive loss of cognitive ability. There are many such illnesses, which have at present no known cause and no cure, and they initially affect different parts of the brain: people with Alzheimer's disease have difficulties with short-term memory, but other illnesses can affect speech or reading and writing. However, they have in common their progressive nature, and that more than one part of the brain is affected. Together they are known as the dementing illnesses; they are more common in the elderly, but can occur in younger people, though they are rare.

All the illnesses are progressive but the rate of progression can vary a great deal. Initially people with the illness can function normally in society; working, driving, socialising and caring for themselves in the way we all consider normal. Eventually they may end up as helpless as a baby. This change can occur in a few years, or be spread over a decade or more. Hitherto there has been no way of predicting whether the disease will progress slowly or quickly; whether it depends on the age of the patient, their gender, or other factors. There are known risk factors which are associated epidemiologically with a higher incidence of disease; it would be interesting to see if these factors are associated with a different rate of progression.

I try to model the rate of decline using data from the OPTIMA project. Although people with dementia do not enter the study until their illness has progressed sufficiently to cause problems with activities of daily living, until their illness all were individuals managing their own affairs, and living a normal life. It is therefore reasonable to assume that they would score close to full-scale on cognitive tests, as do the Optima controls. At the end of their illness, their score is 0, or would be if the interviewer persisted with the test. When their score is about mid-scale, the decline is approximately linear. So we know a model of the decline must look like figure 1.1. Obviously there are no data about the onset of the illness, because the illness is only apparent when symptoms are sufficiently severe to cause problems in daily life; data from the end stage indicates that the decline slows towards the bottom end of the scale and certainly people can survive for some years with very little cognitive ability remaining. Hence it seems reasonable to model the data with the simple inverse S-shaped curve of a logistic function.

The covariates which I would like to consider as possibly affecting the course of the illness are:

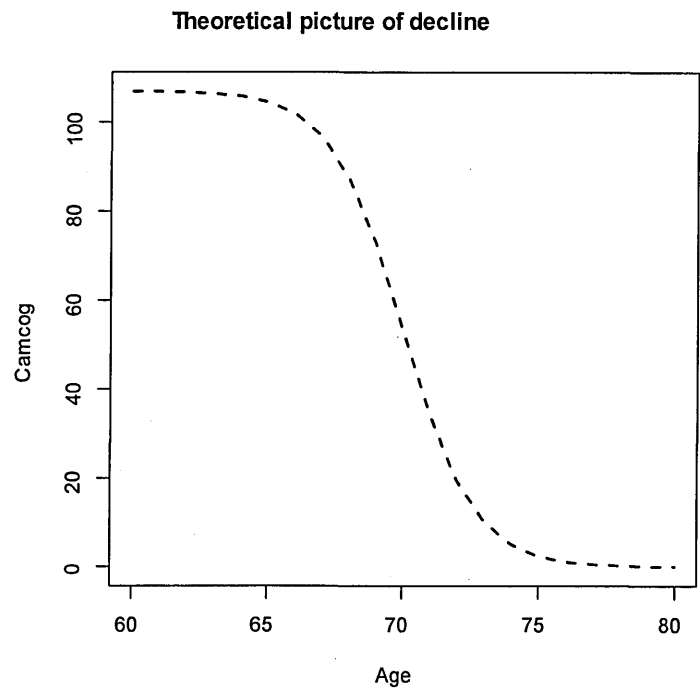


Figure 1.1: Theoretical picture of the decline

- Diagnosis [50];
- APOE genotype [58];
- Age at midpoint of the illness;
- Age at which symptoms were first noticed;
- Levels of certain chemicals in blood and cerebrospinal fluid [52];
- Cardiovascular status [27];
- Gender [2].

Having such a model of the decline has more than theoretical interest. These are real illnesses affecting real people, who initially often have insight into and understanding of their condition. Knowing the likely speed of progression of their illness helps them, their families and the professionals looking after them plan the help that may be needed. It is also important to understand and be able to predict the speed of decline, in order to test if the drugs which are now available do reduce the speed of degeneration.

Any prediction that could be made at an early stage, preferably at the first visit to a specialist, would be very useful. Of course, individuals with the illness, and their families, do not have to know the prediction if they wish not to. Information available at first visit or shortly afterwards includes:

- Current age;
- Age at which symptoms were first noticed;
- Gender;
- Cardiovascular status;
- Current cognitive ability;
- Levels of chemicals in blood and cerebrospinal fluid;
- APOE genotype.

In chapter 2 of this dissertation I give an overview of the dementing illnesses, considering their history, diagnosis, prevalence, the difficulty of measuring the progression of these illnesses and the current state of research into the rate of decline. In chapter 3 I look at the data collected by the Optima project, which I have used as the basis for the rest of the dissertation. In chapter 4 I consider the individual patients, and try to model the decline of each with a logistic model. Encouraged by the success of this model, in chapter 5 I consider variations between patients, and develop a method of comparing data from such a disparate population. In chapter 6 I develop a fixed-effects model incorporating the amalgamated data from all the patients. In chapter 7 I use two different random-effects models to look for commonalties in the data. These models are theoretically preferable, as they treat each patient as an individual, but look for patterns in the covariates. Chapter 7 gives a critical evaluation of the methodologies. In chapter 8 I develop ideas of what the results of the models mean in terms of how the decline of an individual patient is affected by the covariates. In chapter 9 I use the results of the models to calculate a correction to each individual cognitive score, and produce a plot of the corrected Camcog values which allows me to assess the effectiveness of the model. In the final chapter I draw conclusions from what I have shown earlier.

Chapter 2

Background

2.1 Dementia

The WHO International Classification of diseases declares:

Dementia is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is a disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement. Consciousness is not clouded. Impairments of cognitive function are commonly accompanied, and occasionally preceded by deterioration in emotional control, social behaviour or motivation. [45]

2.2 History

Alois Alzheimer observed a patient, Auguste D., a 51-year-old woman, in 1901 [1]. She was suffering from cognitive and language deficits, auditory hallucinations, delusions, paranoia and aggressive behaviour. When she died in 1906 Alzheimer examined her brain, and described pathological changes in the tissue, particularly amyloid plaques (depositions of an insoluble protein) and neurofibrillary tangles. It was known at the time that similar changes occur in the brains of elderly people, but not to such a marked extent, and Alzheimer's disease (AD) was recognised to be distinct from the changes in cognition that occur normally in the elderly. The patient Alzheimer described was young; some decades later [65] it was realised that similar symptoms occurred in more elderly patients, and that 'senile dementia' was in most cases AD. Nonetheless, Jobst et al in 1994 [33] and Mitnitski et al in 1999 [41] felt obliged to point out the differences both clinically and pathologically between Alzheimer's disease and normal aging.

A few years earlier in 1892, Arnold Pick described an illness causing atrophy in the frontal and temporal lobes of the brain, Alzheimer studied brain tissue from such patients, and described 'ballooned' neurons and argentophilic globes (Pick cells and Pick bodies). This illness was named Pick's disease by Onari and Spatz in 1926 [44]. Gradually it was realised that illnesses with similar symptoms, but none of these pathological changes, were much more common, and clinical and pathological diagnostic criteria for Fronto-temporal dementia (FTD) were described [7]. To confuse matters further, FTD is split into three conditions: frontal lobe degeneration (FLD), Pick's disease, and

motor-neuron disease (MND). FTD is also known as dementia of the frontal lobes or FLD.

In 1923 Friedrich Lewy described a type of dementia associated with Parkinson's disease, again with specific changes in cortical tissue now known as Lewy bodies. This illness is now known as dementia with Lewy Bodies (DLB).

Vascular dementia was originally thought to be a type of dementia caused by many small strokes, and it was also known as 'multi-infarct dementia'. Recently it has been realised that few patients with dementia have only vascular symptoms. Many elderly patients with AD also have cerebrovascular disease and the usefulness of 'vascular dementia' as a diagnosis is now being questioned [63].

Other types of dementia, e.g. Korsakoff's syndrome, kuru or Creutzfeldt-Jakob disease (CJD), cortico-basal dementia, dementia associated with Huntington's disease and HIV/AIDS dementia were all described over the course of the 1900s. All are also described by patterns of clinical symptoms in life, and specific pathological changes observed in the brain tissue after death. With the exception of a very few rarer dementias (in particular Korsakoff's syndrome, which is due to chronic alcohol abuse) and CJD (which is due to contact with a malformed protein or prion) dementias generally have no known cause. There is a very small group of people with young-onset Alzheimer's disease which is known to be linked to a specific genotype [20]. However, even in this group, where it is possible to predict who will develop the illness and who will not, there is no possibility of a cure. Drugs to slow the progression of the illness have only just been developed, are suitable only for AD and DLB, and are not effective in all patients.

Young-onset dementia (also referred to as early-onset dementia) is defined as dementia which occurs before the patient is 65 years old. There is no particular medical reason for this distinction; it is more a social and political definition linked to the usual age of retirement. It is nevertheless a useful distinction.

2.3 Diagnosis

The first thing to notice is that dementia itself is not an illness; it is a syndrome or collection of symptoms. According to Harvey, there are more than 200 neurological diseases which can be associated with dementia [22]. There are also other conditions which can cause similar symptoms (e.g. depression, brain tumours, some thyroid disorders), some of which are treatable. During the diagnosis, it is therefore extremely important to check for and, if necessary, treat these conditions.

The diagnostic process starts with interviews with the person suspected of having dementia, and their partner if possible, to take a recent history of the problems which led them to seek medical assistance. Various neuro-psychological tests will follow, some of which are similar to intelligence tests. These tests are designed to pick out any changes in normal brain function, e.g. memory deficits, difficulties with word-finding or manipulating numbers, problems with understanding simple instructions, personality changes, and to establish that more than one area is affected, and that the person is

not delirious or otherwise of impaired consciousness. Scans (MRI, CT and SPECT) are also useful in showing any abnormality in the brain.

Dementia can only be considered as a diagnosis once it has been established that there are deficits in multiple domains, and that these have been present for some months. The treatable conditions which can mimic these symptoms should be tested for, and treated if present.

There is still no absolute test for dementia; a diagnosis comes after excluding all other possibilities, and by considering the pattern of symptoms.

To summarise: the dementias are

- neurological diseases causing a loss of cognitive abilities in multiple areas;
- often progressive, but always irreversible;
- only diagnosed with certainty by examining brain tissue;
- differing by orders of magnitude from loss of abilities caused by normal aging.

All the dementias described have typical patterns of symptoms. The early stages of Alzheimer's disease are normally marked by a deficit in short-term memory, though long-term memory is often preserved until later in the illness. The frontal lobe dementias are marked by a loss of language ability, or by a change in character and the ability to see the effects of one's actions. CJD progresses much more rapidly than is typical for other dementias, and also affects the balance and muscle control. Visual hallucinations often occur in Lewy-body dementia, and the loss in abilities can vary noticeably over a few hours. In almost all cases, the illness creeps on slowly and insidiously over a few years, and may be difficult to recognise and diagnose.

Although all the dementias are eventually totally disabling illnesses, they are not usually fatal. In patients with dementia, death is often due to an infection (most commonly pneumonia) or accident, and the death certificate will show the infection or accident without recording the underlying dementia.

2.4 Prevalence

Although the dementias can affect people from teenage years upwards, they are extremely rare at this age. Harvey [23] has estimated the prevalence of dementia in people under 65 at 54.0 per 100,000 (0.054%) (95% CI 45.1 to 64.1 per 100000). In people over 65 it is progressively more common. Alzheimer's disease is the most common cause of dementia at all ages, but it is much more common in the elderly, and other dementias are proportionately more common in younger people. A graph showing the prevalence at ages over 60 is shown in Figure 2.1, using data from the World Health Organisation ([45]).

The dementias are eventually totally disabling illnesses, and people with dementia need a lot of individual care in the later stages. As the world population ages, the number of people with dementia is likely to increase, and their need for care will be

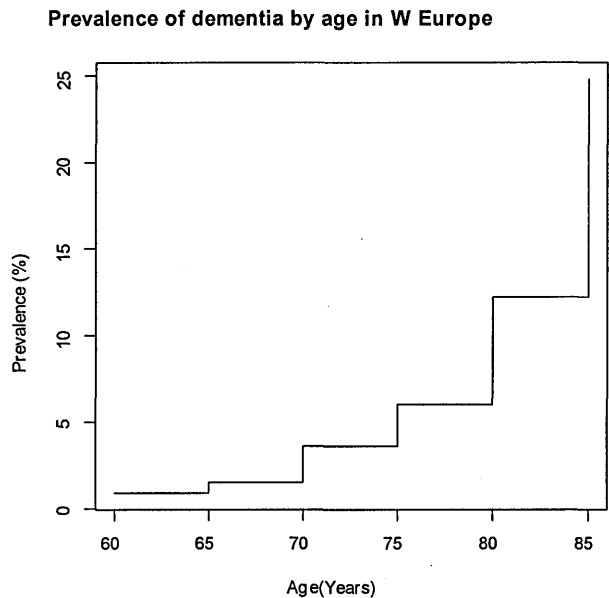


Figure 2.1: Prevalence of dementia by age

very high. The same WHO report has estimated the total number of cases of dementia, both in Western Europe, and worldwide, over the next 40 years, and the numbers they predict are shown in Figure 2.2.

Despite the nature of the illness, and the serious economic burden patients place on society, dementia has been a neglected field compared with, say cancer. In 2006, the UK Clinical Research Collaboration (UKCRC) analysed the spending on research by disease category [67]. Their study found that approximately 16% of all UK research funding was spent on neurological disorders (dementia, Parkinson’s, epilepsy and MS) compared with 27% on cancer.

2.5 Epidemiology

While it is not yet possible to predict who will develop dementia and who will not, there are known risk factors which increase the probability that a person will develop the syndrome, and factors which are known to have a protective effect. The biggest risk factor is described in the section above, and is age. This has such a strong effect on the chance of an individual developing dementia that it tends to confound other studies (e.g. smoking). Other known or suspect factors are described below.

2.5.1 Family history of dementia

First-degree relatives of people with AD have an increased risk of developing the disease [68]. This risk is around 1.03 times the population risk, and is a stronger effect for relatives of young-onset AD patients. There are also a few very rare families with an autosomal dominant mutation where the risk is much higher.

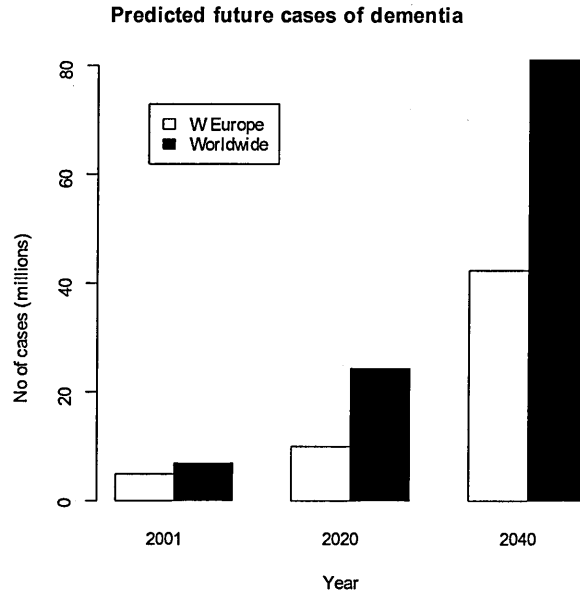


Figure 2.2: Projection of cases of dementia

2.5.2 APOE genotype

The APOE gene has 3 alleles: APOE2, APOE3 and APOE4. The APOE3 allele is the most common. Caucasians with 2 copies of the APOE4 allele have a 15 times higher risk of developing AD compared with people with two copies of the APOE3 allele. Those with one APOE4 and one APOE3 have a three times higher risk [17]. The risk seems to be lower in non-Caucasians. The presence of the APOE4 allele is not sufficient to cause AD.

2.5.3 Down's syndrome

The genetic mutation associated with Down's syndrome causes a greatly increased risk of AD. By the age of 40, virtually all people with Down's syndrome show the neuropathological changes of AD [73], and by the age of 60 approximately 40% have developed AD [24]. It can be difficult to diagnose dementia in adults with learning disabilities, as the standard cognitive tests cannot be used and different tests are needed.

2.5.4 Head injury

Early studies found that a history of head injury with loss of consciousness was 80% more common in AD patients than in controls [42]. However, this was a retrospective study which relied on relatives providing information about the patient history. This may have been a source of recollection bias, as a head injury followed by the onset of dementia may be more memorable than one not followed by dementia. More recent studies which used medical records have not always found an association [6], [57].

2.5.5 Hormone Replacement Therapy

Yaffe et al in 1998 found that oestrogen replacement therapy reduced the risk of AD by around 30% [72]. Unfortunately the result must be treated with some caution, as the groups of women using HRT, and those not using HRT are not necessarily otherwise equivalent, particularly in level of education. A recent trial of oestrogen treatment for those with mild to moderate AD showed no difference between the treated and untreated group [43].

2.5.6 Non-steroidal anti-inflammatory drugs (NSAIDs)

People with rheumatoid arthritis who take NSAIDs as a treatment for arthritis, have a reduced risk of developing AD [40]. Unfortunately randomised clinical trials to show if this protective effect is real are difficult, because of the side-effects of the drugs.

2.5.7 Aluminium

High levels of aluminium in the diet have long been associated with an increased risk of AD. Early studies which showed this association were poorly designed, but a more recent study [53] has shown that there may be such a link. An unintended experiment was started when, in 1988, an accident at a water treatment plant resulted in approximately 20,000 people being exposed to very high levels of aluminium sulphate in their drinking water. In 2004, one of these people died of young-onset dementia, and a post-mortem study of her brain showed AD-type depositions, and high levels of deposited aluminium [16]. Interestingly, the patient's genotype was APOE4/4.

2.5.8 Smoking

Graves et al in 1991 found a 20% reduction in AD in smokers [21]. In 1998, Ott et al found the opposite effect, with smokers at twice the risk of developing AD [47]. Given its other effects, smoking is probably best avoided.

2.5.9 Neurocognitive reserve

In 1996, Snowdon et al published a study comparing verbal ability in early life with AD pathology post-mortem [59]. He studied a group of nuns, who had written autobiographies as young adults, and many years later donated their brains. All those with confirmed AD had low verbal ability, compared with none in the group without AD. Other studies have shown that people with a lower level of education have a higher rate of AD [61] [71]. This may be confounded by the tests used to measure cognitive capacity (less well-educated people tend to achieve lower scores than the highly-educated), but has led to the theory that better-educated people are better able to compensate for any disease impairment.

2.5.10 Diet

It has been known for some time that AD patients tend to have lower levels of B12, and higher levels of serum folate [11]. Optima has just embarked on a 2-year double-blind randomised clinical trial, treating patients diagnosed as having MCI with either a placebo or a combination of B-vitamins and folic acid, to see if the vitamins do offer some protection against further cognitive decline.

2.6 Measuring the progress of the illness

There is considerable variability in the pattern, progress and outcome of all the dementias. Time between diagnosis and death varies from 1 year to 16 years for AD patients, with a mean of 5-6 years [66]. The time from initial approach to GP to diagnosis can also vary markedly; in the Optima patients it can be as short as a few months or as long as several years. There is also a time when the symptoms are gradually worsening, before the patient seeks medical help. There are two common approaches to trying to measure the rate of decline of people with dementia; using some kind of cognitive measurement or using a global rating scale which attempts to measure how well the patient functions within society.

Typical cognitive scales are the Mini-mental state exam (MMSE) [19], the cognitive component (Camcog) of the Cambridge Disorders of the Elderly Examination (Camdex) [55], and the cognitive subscale of the Alzheimer's Disease Assessment Scale - (ADAS-Cog) [54]. The MMSE scale is 0-30, the Camdex 0-107 and the ADAS-Cog 0-70. For the Camcog and MMSE, a higher score means greater cognitive abilities; for the ADAS-Cog scale a lower score means greater ability. The MMSE is in fact a subset of the Camdex, and is most frequently used because it is very quick to administer. It is even possible to administer a similar test over the telephone - the TICS-M test [13]. These cognitive tests are relatively simple to administer, and provide a good objective assessment of the cognitive abilities of the person, but this does not necessarily bear much relationship to how well a person can function in caring for themselves, and in society. Changes in these cognitive scales can be apparent after only a few months. The rate of change is always quoted in 'points per year', and the assumption is that the rate of change is linear across the range of the test. Typical decline rates are quoted as 2.5 MMSE points, 12 Camdex points and 8-9 ADAS-Cog points per year [66]. The same reference a little later says '*individual rates of decline are non-linear, being slower at the milder stage, but accelerating as the dementia progresses*'. Yet the quoted rates of decline are not given any range of scores for which they are valid.

There is a multiplicity of scales designed to measure how well the person with dementia can function within society. Such scales are the activities of daily living (ADL) scale [35], the Blessed Dementia scale [4], the instrumental activities of daily living (IADL) scale [37] and the functional assessment questionnaire (FAQ) [48]. The Barthel scale [39], is used in some early papers, although this scale is designed to measure physical abilities. Changes in these scales can take longer to become apparent, and the tests are not as easy to score. The tester frequently has to rely on information given by the

person with dementia, and this information cannot always be relied on: “*The patient may say, ‘I go out shopping every day...my memory is fine...I have no difficulty with my money...I am making really good meals...I don’t know why my daughter worries so much about me.’ In reality, the patient may be crippled, living up four flights of stairs, with no food in the larder, and the gas cut off for non-payment of bills, while money is found under blankets and mattresses.*” [3]. If the information comes from either a questionnaire filled out by the partner of the person with dementia, or a structured interview with the partner, what is being measured is the partner’s perception and not necessarily the real abilities of the person with dementia. Despite these limitations, these tests assess how well the person with dementia can function, which is of more interest to the patient and their family. Although in this dissertation I have concentrated on modelling the cognitive scores, it would be very interesting subsequently to compare the data on activities of daily living which Optima collected at the same time as the cognitive tests.

The most common overall assessment scale is the Clinical Dementia Rating Scale (CDR) [29], which measures cognitive and functional abilities, and rates a person with dementia on a 5-point scale from “not impaired” to “severely impaired”.

2.7 Comparing rates of decline

A search of PubMed in May 2007 for the words ‘rate’, ‘decline’ and ‘dementia’ offered 530 relevant papers; the oldest dating back to 1978. A search for ‘rate’, ‘progression’ and ‘dementia’ found a similar number. I have considered abstracts of 159, of which 66 are relevant to the study of decline rates in dementia.

In 1982, Rabins and Folstein compared survival rates for people with dementia against those with delirium on admission to hospital [49], and in 1987 Rosen et al compared rates of cognitive decline for people with dementia against people with other Parkinson’s disease. The paper “Measuring the course of Alzheimer’s disease. A longitudinal study of neuro-psychological function and changes in P3 event-related potential” by St Clair et al [10] sounds promising, but in fact takes two measurements of cognitive ability one year apart and draws conclusions about rate of decline from those. Ortof and Crystal [46] in 1990 again study AD patients with “at least” 3 cognitive measurements over “at least” one year, and assume a linear rate of decline over the course of the illness; none of these papers makes any mention of the stage of the illness, or the actual score of the patients they have considered.

The first paper to describe the course of AD over the course of the illness that I have found is Stern et al in 1994 [60]. He used the ADAS-Cog scale to measure the cognitive skills of people with dementia and a similar control group without dementia; taking the measurements every 6 months for up to 90 months. He found no decline in the control group (in fact, a slight increase, presumably due to the learning effect), and a variable rate of decline in the demented group, with decline being fastest in the middle part of the scale, and slower for both mildly and severely demented patients. The same author two year later [62] used an inverse growth curve to model the cognitive decline

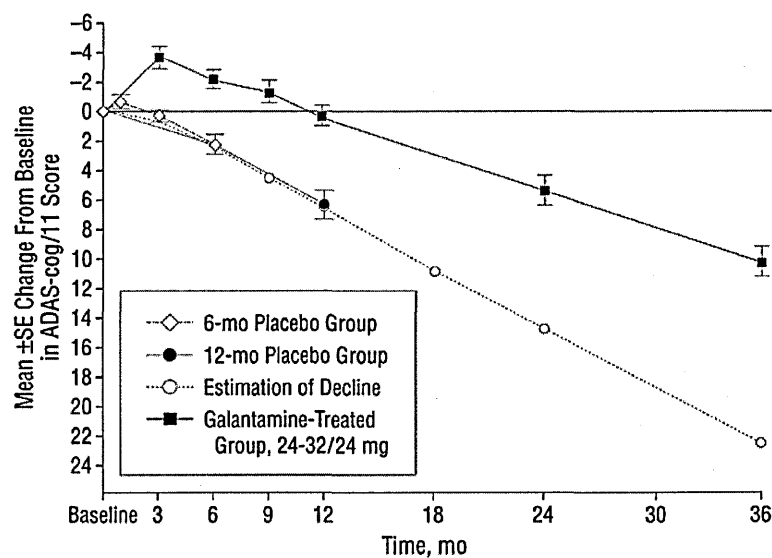
and ADL scores of 236 patients with probable AD, measured every 6-months over 5 years. They found an inverse S-shaped curve was appropriate for the cognitive decline, with a more linear decline in the ADL scores. They make no attempt to consider any factors which may affect the rate of decline; they are more interested in comparing the differing scales.

In 1994 Jacobs et al [30] followed a group of patients with probable AD for 2 years. The group was split into young-onset and older-onset patients, with a dividing line at 65 years. The groups were comparable in cognitive scores at the beginning: after 2 years the young-onset group showed a greater decline than the older group. The analysis controlled for symptom duration, gender, family history of dementia, and baseline cognitive scores, but not for other possible confounding variables (e.g. APOE status or initial homocysteine level, both of which may affect the rate of progression). Their findings were confirmed by Teri et al in 1995 [64], who also found faster rates of decline in young-onset patients. They also found a faster decline as the illness progressed: they followed patients for up to 5 years. If their patients were moderately demented at the start of their study, at least a few must have been severely demented after 5 years, and so out of the stages of dementia where the rate of decline does approximate to linear, yet there is no comment on the final cognitive score of their patients.

In 2003 Holzer et al [26] studied a group of probable AD patients over 5 years, and reached the hardly surprising conclusion that a faster rate of decline of MMSE score in the first year was related to a higher rate of dependency levels in later years. Holmes et al [25], Carcaillon et al [8], Kleiman et al [36] and Chuu et al [9] all take two or three measurements of a cognitive scale, and use them to calculate a rate of decline which is assumed to be linear, and then test whether this rate of decline is correlated with other variables. This is only a valid approach if the initial cognitive scores of all patients are similar, and this point is never mentioned.

This is a pattern which is replicated time after time: most of the 66 relevant papers take measurements of the decline rate in dementia as “X points of Y scale per year”, irrespective of the point on the scale at which the decline occurs; or the timescale for the measured decline. There is a tacit assumption that a decline from (e.g.) 30 MMSE points to 29 in 6 months is equivalent to 20 to 18 in 1 year, or 10 to 6 in two years. This despite the fact that it was recognised from early on that the decline is not linear, especially in the early and later stages of the illness, and that treating the decline as linear can give misleading results [34]. With the current emphasis of research on people who may be at the early stages of dementia (those with Mild Cognitive Impairment or MCI), it is especially important to recognise that decline across the whole scale is not linear, and that a ‘fast’ rate of decline of 3 MMSE points per year in the mid-stages of dementia (MMSE 10-20) is not necessarily equivalent to a decrease from 29 to 26 MMSE points over a year.

Change from baseline in Alzheimer's Disease Assessment Scale-11-item cognitive subscale (ADAS-cog/11) scores of patients treated with galantamine hydrobromide for 36 months



Raskind, M. A. et al. Arch Neurol 2004;61:252-256.

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Figure 2.3: Results of trial with Rivastigmine

2.8 Measuring the efficacy of drugs

There are now several drugs which are recommended for treatment of Alzheimer’s disease in early to moderate stages. It was observed that the brains of AD patients were low in the neurotransmitter acetylcholine [5] Drugs were developed which can reduce the rate at which this chemical is destroyed in the brain: these are the cholinesterase inhibitors donepezil, rivastigmine and galantamine . The papers which test the clinical efficacy of these drugs mostly do not mention the “rate of decline”. Instead, they select a group of patients in the relevant stages of the dementia; allocate them at random to a treated group or a placebo group, and monitor their progress over a few months - typically 6. This is a valid approach, and the results produced are impressive, though unfortunately only for some patients [51]. However, once the 6-month trial is completed and the results are known, it is no longer ethical to keep some patients on placebo, when the treated patients show at least a slower decline. If the trial is continued, all patients are now given the drug, and there is no placebo group to compare. In this case, the researchers invariably show a “predicted decline”, which continues at the same rate as the group on the placebo, as shown in Figure 2.3. This is, of course, a valid approach during the middle stages of the illness. However, the drugs have now been licensed for use for 10 years, by which time many AD patients will have reached the ‘floor’ of any cognitive scale. It is important at that stage to allow for the non-linear decline.

Chapter 3

The data

The Optima project is a longitudinal study of people suffering from some sort of dementing illness. It has been running since 1988, and has recruited 780 people (to December 2006), of whom about 500 suffer from a progressive degenerative neurological illness which affects their cognitive abilities. Ethics approval was granted by the Oxford Ethics Committee, and the project has Corec number 1656.

At the initial visit, patients are given a full physical exam, a series of cognitive tests, and an interview exploring family history and current problems of everyday living. Blood is taken for various tests, and, if the patient is willing, a lumbar puncture is performed to take a sample of cerebrospinal fluid (CSF). Various scans such as magnetic resonance imaging (MRI), computer tomography (CT), single photon emission computed tomography (SPECT) may be carried out. The patients genotype will be checked for a few alleles which are known to affect the incidence of AD. At the same time, the patient's partner will be interviewed about problems faced by the patient and themselves as a result of the dementia, and the partner may be given advice about available help. Subsequently patients are seen at approximately 6-monthly intervals, and at each visit various cognitive tests are performed, the patient is interviewed and so is a close relative or friend who knows the patient well. The majority of the Optima patients live within the Oxford area, and were referred to Optima because they were diagnosed at Oxford, or came under the care of an interested GP within Oxfordshire. Not all patients who were referred agreed to join the project; hence this cannot be considered a random sample.

The demographics of the cohort is described in table 3.1. It can be seen that the cohort is evenly split between males and females, and that the mean ages at first visit are surprisingly similar, especially since there was no selection process involved. Unfortunately Optima did not collect sufficient data to ascertain the socio-economic class of the individuals concerned, but information on educational level was collected. This is a population where the school leaving age has changed several times, and although people were asked how many years they spent in further education, no record was made of whether this was full-time or part-time. Hence the table shows the number of participants who have spent any time in further education. It can be seen that this population has a higher educational level than average. In view of the theories about educational level and cognitive reserve, caution should be exercised in applying the

results to the general population.

	Male	Female
Number	62	61
Mean age at first visit	72.1 yrs	72.3 yrs
Time in Further Education	22 (35%)	19 (31%)

Table 3.1: Demographics of Optima patients with dementia

Optima has also recruited a group of about 400 controls (389 June 07) who are interviewed on family history, given a similar physical examination and scans at the initial visit. They are given the same cognitive test as patients, but may also be asked to do more extensive neuropsychological testing. They are subsequently seen every 1 or 2 years to repeat the cognitive tests.

The principal diagnostic test used is the Camdex – the Cambridge Mental Disorders of the Elderly Examination [55]. The complete Camdex has three main sections: a structured interview with the person under review to obtain systematic information about the present state, past history and family history; a range of cognitive tests which constitute a mini-neuropsychological battery; and a structured interview with a partner or other informant to obtain independent information about the person’s present state, past history and family history. The cognitive test is usually referred to as the Camcog. It is used to identify cognitive deficits, so normal healthy people are expected to achieve a score close to full-scale of 107. Someone incapable of understanding or responding to questions would achieve a score of 0. Those suffering from Alzheimer’s disease or similar neurodegenerative illnesses will show a fairly steady decline; those suffering from different illnesses often show a more step-wise decline, when some trauma will produce a sudden decline, with maybe a slight increase or a steady state between events.

Optima has a wealth of data apart from the cognitive test. The partner questionnaire has approximately 150 questions designed to establish how well the person with dementia can function within society and in caring for themselves; to see if there is a family history of this or other illnesses. At the first visit the patients is given a detailed physical examination, blood and cerebrospinal fluid (CSF) are collected and tested for many common components. Whole blood, plasma and CSF are also stored for subsequent study. If possible, CT, SPECT and MRI scans of the brain are taken.

I have chosen to concentrate my analysis on the cognitive score, and a few covariates that are known to affect the prevalence of the disease, and may affect the rate of decline. I have adopted this approach because the cognitive test is the best measured - the activities of daily living reported by patients and partners are subjective measurements, and there are often differences in reports between patient and partner. It is also the approach used in most other research into the decline rates of dementia. However, once the model has been validated, it would be very interesting to compare the cognitive scales with other measures of how well the patient can function.

There is an obvious problem with the data, in that there are currently no data at the start of the illness. Without embarking on a very large prospective study, it is impossible to collect such data. Fortunately, even in the very elderly population, these illnesses do not affect the majority of people. For those aged 45-64 years, the prevalence

is 98.1 per 100000 (95% CI 81.1 to 118.0 per 100,000) [23]. It is, however, reasonable to assume that people with dementia were, before their illness, typical members of the general population. Recently a few of the Optima controls have been diagnosed with possible AD, so a future study may be able to study the full course of the illness.

Patients do not enter Optima until they have already received a diagnosis of dementia from a hospital consultant. The illness has already caused them sufficient problems in normal living to drive them to see a GP. The GP has referred them to a consultant, and the consultant has made a diagnosis. This may be a protracted process, especially for the younger people, for whom these illnesses are comparatively rare. Hence the delay before presentation can be 2-3 years or more.

Some typical individual plots of the Camcog score of an individual patient over time are shown in Figure 3.1. In order that the graphs can easily be compared, I have plotted the time scale so all graphs show a 10-year period, with the midpoint approximately at the midpoint of the assessments, and the Camcog axis shows the full Camcog scale. Patients are identified by their Optima ID. One plot for a control subject (optima ID 248) is included to show the expected continuation at close to full scale.

Initially I considered all the Optima patients with a diagnosis of some form of dementia whose Camcog scores included values both above and below the midpoint of the scale. There are 154 such patients. Boxplots of the age at which these patients were first assessed by Optima, and the number of visits per patients, are shown in Figures 3.2 and 3.3.

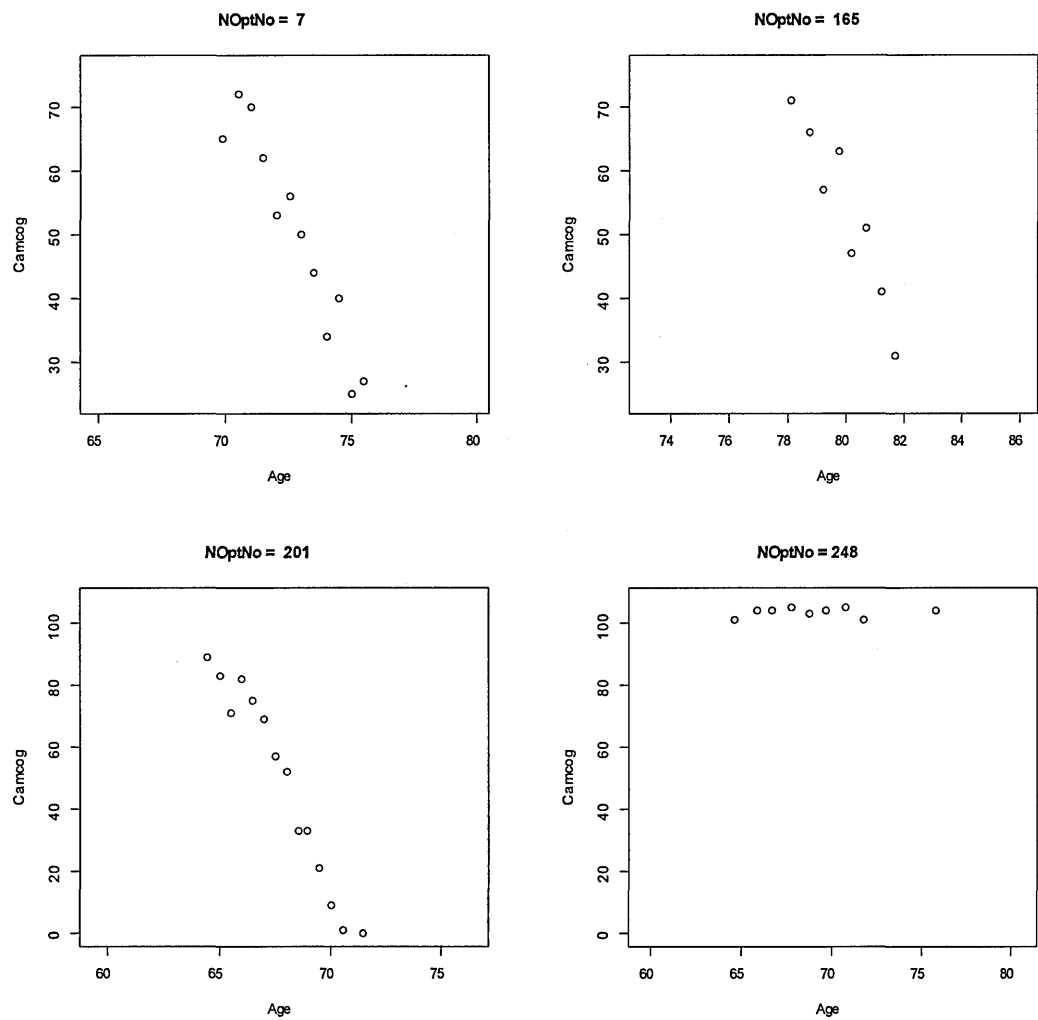


Figure 3.1: Some sample individual Camcog scores over time



Figure 3.2: Age at First Visit

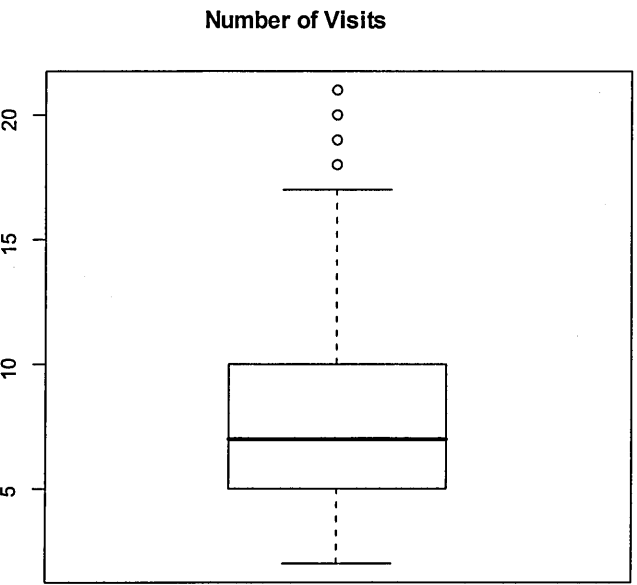


Figure 3.3: Number of visits per patient

Chapter 4

Fitting individual patients

The approach of many people is to model the decline as linear[25]. This model seems to describe the central part of the data quite well, but has some obvious problems. The real Camcog scale has upper and lower limits; and therefore can never be fitted sensibly with a straight line, nor is it an appropriate form for fitting the interesting area of the low Camcog scores.

We know from the data that, assuming the patient is sufficiently well to remain in the study, the Camcog score eventually levels out at or close to zero. It can also be assumed that prior to the illness, the patient would have had a score close to 107. The mean of the scores from the Optima controls is 99. Unfortunately there are no data for any of these patients for the early part of the illness, because they only enter the study once a dementing illness has been diagnosed. One of the criteria for such a diagnosis is a Camcog score < 80 . Optima is currently working with patients in the earlier stages of what might prove to be a dementing illness, but these data are not yet available.

A curve which has the appropriate S-shape is the binomial, or logistic curve. This is often used to model a binomial proportion, but it can be adapted to model the Camcog, if the Camcog is regarded as a proportion of the full-scale value. Using this family of curves means making an assumption that the curve is symmetrical about the midpoint. There is certainly no reason to doubt this model, and there is no evidence for asymmetry.

In order to fit a generalised linear model with a binomial proportion response, the Camcog values were transformed by dividing by the possible full-scale value:

$$Camcog / (TotalQuestionsAsked - Camcog)$$

This value is a measure of how cognitively impaired the person answering the Camdex is; someone who answers 100 question correctly will achieve 14.29; someone who answers no questions correctly will achieve 0. This value will be referred to as the **impairment index**.

The value "Total Questions Asked" is normally 107 (the maximum Camcog score). A casual conversation with one of the nurses who conducted Camcog questionnaires revealed that, if the patients were relatively impaired (eventual score likely to be $< 50\%$), she did not complete the questionnaire. This was against the training she had been given, but I could not contact all the nurses Optima has employed to find out

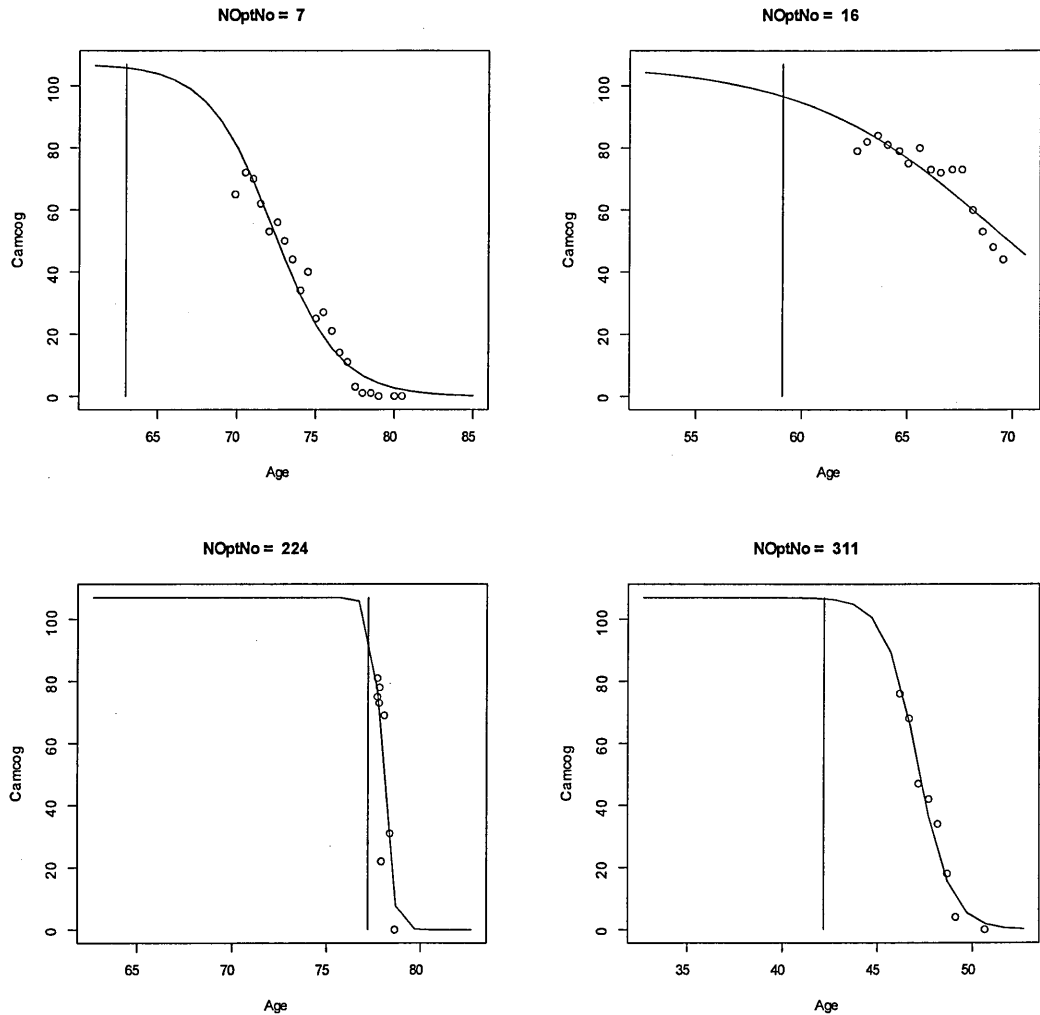


Figure 4.1: Some sample logistic regression models

what their practice had been. I did look at the recorded interviewer, to see if there was any correlation between interviewer and number of incomplete questionnaires, but there was no such correlation. However, in any case the interviewer records which questions were not asked, so that the maximum attainable score is also known.

The model was fitted using the binomial variant of the R generalised linear model function, as described in section 1.1. A series of plots for 4 individual patients is shown in Figure 4.1 below. Again, the plots are all drawn to the same scale; the raw data are plotted as points, and the model as a curved line. The plots also show a vertical line close to the point where the Camcog decline begins. When patients first visit Optima, they are asked at what time previously they first became aware of problems. This line is drawn at that age.

As shown above, the model gives quite a good fit for patients when considered individually. It is clear, though, that the curves vary considerably from one person to another, both in the age at which the illness occurs, and the rate of decline. This is not surprising, as all the patients are different, with differing types of illness, gender, general

health, genotype, etc. It is known that some of these factors affect the likelihood that an individual will develop dementia; maybe they also affect the rate of progression. Further modelling is required to see if there is any consistency or predictability for these differences.

Chapter 5

Determining a time scale

The rate of decline can vary markedly from patient to patient; some will lose 50 Camcog points per year, and others only 5. Patients typically are only referred to Optima when their illness has already affected their cognitive abilities, so the typical initial score is 80 – 90. Patients and relatives are asked when they were last “normal”, but this measure is extremely subjective. So there is no common start point for the measurements taken. The end point is equally uncertain; both patients and testers can find the test distressing during the later stages of the illness, hence no measurement is taken; some patients no longer wish to continue participating, and some unfortunately die. The illness can affect people at different ages; hence absolute age cannot be used as a scale. Patients were recruited throughout the duration of the project, so some measurements date back to 1988, and some only start in 2004. Hence finding a single time scale to allow patients to be compared is a non-trivial exercise.

This problem was solved successfully by using the approximate linearity of decline around the middle part of the progression of the disease to estimate the age at which each patient would have achieved a Camcog score of 53.5 (mid-scale), calling this AdjAge_0 , and then using it to calibrate each patient’s age measurements. Thus the statistical analysis uses $\text{Age} - \text{AdjAge}_0$ as its measurement scale for age.

The mid-scale point was chosen because:

- The Camcog measurements for most patients cover values that range above and below the midpoint score of 53.5
- The Camcog decline is not linear, but it approximates to linear in mid-scale.

I used the R statistical package (version 2.4.1) to analyse the data.

5.1 Theory behind the linear model

The Camcog score and age for one Optima patient are plotted shown in Figure 5.1 below. I have only shown the central part of the data, i.e. Camcog scores ≥ 25 and ≤ 75 .

The assumption is that there is an underlying linear relationship here. i.e.

$$C = \alpha + \beta.Age$$

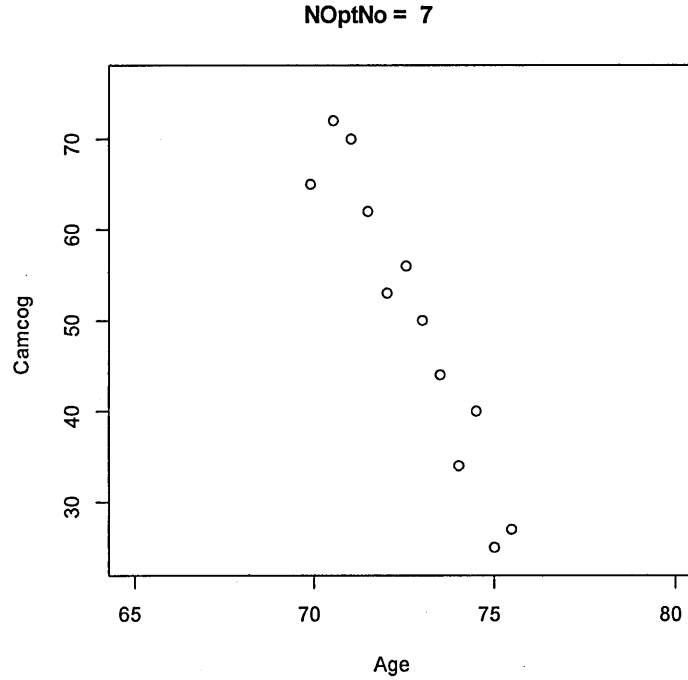


Figure 5.1: Central part of the decline for one patient

but with a random error on each point i :

$$C_i = \alpha + \beta \cdot \text{Age}_i + \varepsilon_i$$

where the errors ε_i are independent of each other, and distributed normally with mean 0 and standard deviation σ . More generally, the model is

$$Y_i = \alpha + \beta \cdot x_i + \varepsilon_i, \quad i = 1, 2, \dots, n$$

where Y_1, Y_2, \dots, Y_n are observed random variables, x_1, x_2, \dots, x_n are specified and $\varepsilon_1, \varepsilon_2, \dots, \varepsilon_n$ are non-observable random variables.

x_i is the *explanatory* variable (corresponding in my data to Age);

Y_i is the *response* (corresponding in my data to Camcog);

ε_i is a *residual*.

Since each ε_i has distribution $N(0, \sigma^2)$, then

$$E[Y_i] = \alpha + \beta \cdot x_i, \quad V[Y_i] = \sigma^2, \quad i = 1, 2, \dots, n$$

Rewriting equation (1) in matrix notation gives

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\theta} + \boldsymbol{\varepsilon}$$

where

$$\mathbf{Y} = \begin{pmatrix} Y_1 \\ \vdots \\ Y_n \end{pmatrix}, \quad \mathbf{X} = \begin{pmatrix} 1 & x_1 \\ \vdots & \vdots \\ 1 & x_n \end{pmatrix}, \quad \boldsymbol{\theta} = \begin{pmatrix} \alpha \\ \beta \end{pmatrix}, \quad \boldsymbol{\varepsilon} = \begin{pmatrix} \varepsilon_1 \\ \vdots \\ \varepsilon_n \end{pmatrix}$$

$$E(Y) = X\theta, \quad V(Y) = \sigma^2 I$$

, where I is the identity matrix

$$\begin{pmatrix} 1 & 0 & \dots & 0 \\ 0 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 1 \end{pmatrix}$$

The likelihood function of α, β, σ^2 has the form

$$L(\alpha, \beta, \sigma^2; y) = (2\pi\sigma^2)^{-n/2} \exp \left[-\frac{1}{2\sigma^2} \sum \varepsilon_i^2 \right] = (2\pi\sigma^2)^{-n/2} \exp \left[-\frac{1}{2\sigma^2} \varepsilon^T \varepsilon \right]$$

Maximising L , which gives the most likely fit to the estimates of α, β, σ^2 , corresponds to minimising

$$\sum_{i=1}^n \varepsilon_i^2 = \varepsilon^T \varepsilon$$

hence this is known as the method of least squares. Least squares is only equivalent to maximum likelihood if the underlying distribution of ε_i is normal.

$$\varepsilon^T \varepsilon = (\mathbf{Y} - \mathbf{X}\theta)^T (\mathbf{Y} - \mathbf{X}\theta).$$

For this to be a minimum,

$$\frac{d(\varepsilon^T \varepsilon)}{d\theta} = 0.$$

Hence

$$2\mathbf{X}^T (\mathbf{Y} - \mathbf{X}\theta) = 0,$$

so the maximum likelihood estimate $\hat{\theta}$ of θ is given by

$$\mathbf{X}^T \mathbf{X} \hat{\theta} = \mathbf{X}^T \mathbf{Y}.$$

Provided $\mathbf{X}^T \mathbf{X}$ is non-singular, this is

$$\hat{\theta} = (\mathbf{X}^T \mathbf{X})^{-1} \mathbf{X}^T \mathbf{Y}.$$

Using the data from the patient ID no 7 above,

$$\hat{\alpha} = 633, \quad \hat{\beta} = -8.01$$

The data with the fitted line are shown in Figure 5.2.

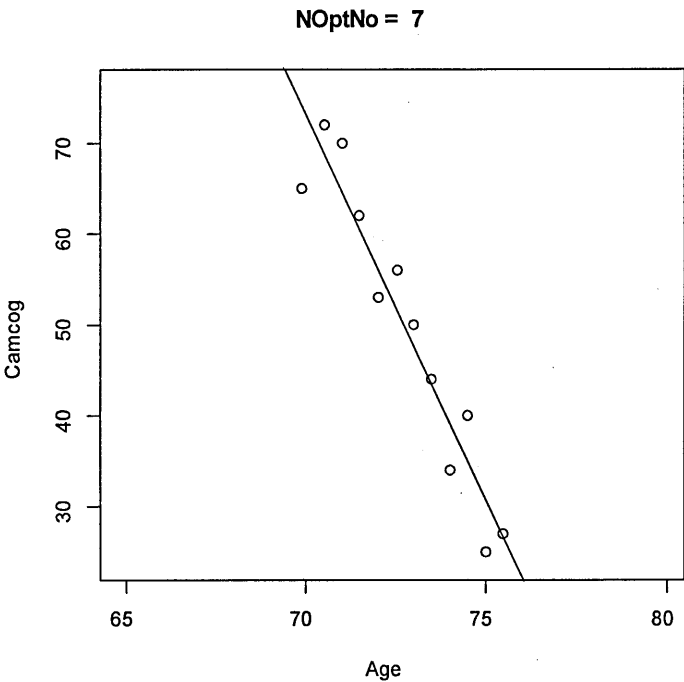


Figure 5.2: Central decline with linear model

5.1.1 Assumptions of the model

To reiterate, the assumptions on which the above calculation is based are:

- the variance of the response is constant;
- the data are well described by the linear equation;
- the distribution of the response is normal.

The first assumption can be assessed by looking at a plot of the residuals of the model against the fitted values. The plot for these data is shown in Figure 5.3: the points seem randomly scattered, indicating that the assumption is valid.

The plot of raw data against fitted model above shows that the basic assumption that the data can be fitted by the given equation seems good. The plot of fitted against residuals shows that the second assumption is also good, in that the points seem to be spread randomly.

The third assumption is checked by looking at a qq plot of the residuals, which should be approximately a straight line. The plot for these data is shown in Figure 5.4: the data does approximate to a straight line.

It is necessary to know the confidence limits of this estimated midpoint. age before it can be used in further calculations. Since a ratio of estimators is involved, Feiller’s theorem[18] was used to calculate the confidence intervals for the midpoint age.

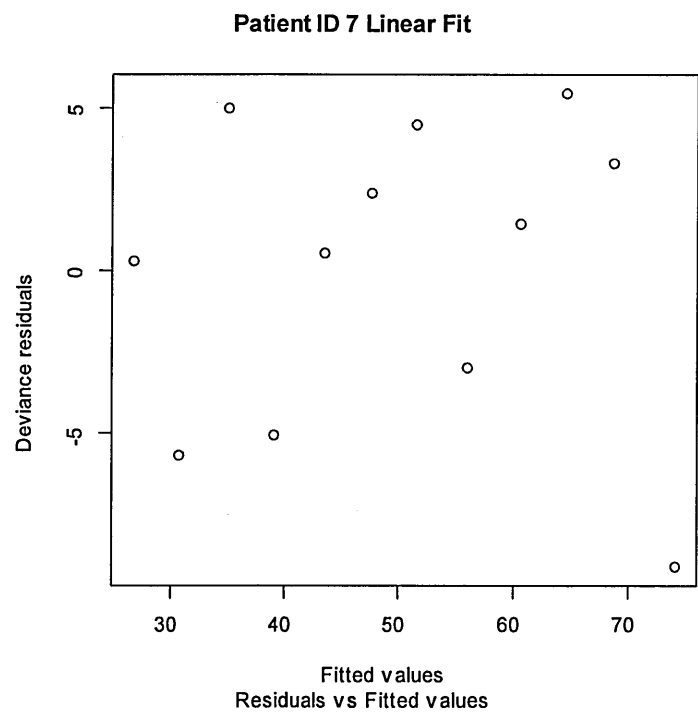


Figure 5.3: Deviance residuals-fitted values for Patient ID 007

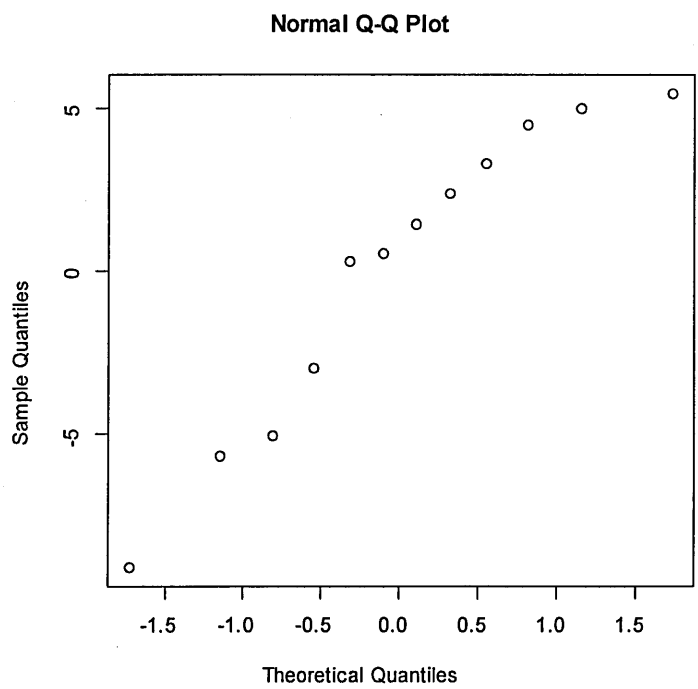


Figure 5.4: QQ plot for linear model

The true value of the midpoint age is given by

$$\gamma = \frac{(C_m - \alpha)}{\beta},$$

where C_m is the midpoint of the Camcog scale (*i.e.* 53.5) and α, β are the true values of the intercept and slope of the model.

The model gives estimates $\hat{\alpha}, \hat{\beta}$ of intercept and slope, $V(\hat{\alpha}), V(\hat{\beta})$ which are their estimated variances and the estimated covariance $C(\hat{\alpha}, \hat{\beta})$.

Consider

$$\begin{aligned} Z &= \hat{\alpha} + \gamma\hat{\beta} - C_m \\ E(Z) &= 0, \quad V(Z) = V(\hat{\alpha}) + \gamma^2 V(\hat{\beta}) + 2\gamma C(\hat{\alpha}, \hat{\beta}). \end{aligned}$$

If m is the 0.975 cut-off value for Student's t -distribution with $n - 2$ degrees of freedom, where n is the number of sample points used, then, using the estimated variance of Z ,

$$P\left(-m < \frac{Z}{\sqrt{V(Z)}} < m\right) = 0.95$$

Thus for the limiting values

$$m^2 = \frac{Z^2}{V(Z)}$$

and substituting for Z gives

$$m^2 = \frac{(\hat{\alpha} + \gamma\hat{\beta} - C_m)^2}{V(\hat{\alpha}) + \gamma^2 V(\hat{\beta}) + 2\gamma C(\hat{\alpha}, \hat{\beta})}$$

Solving for γ gives

$$\gamma = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

where $a = \hat{\beta}^2 - m^2 V(\hat{\beta})$, $b = 2\hat{\beta}(\hat{\alpha} - C_m) - 2m^2 C(\hat{\alpha}, \hat{\beta})$, $c = (\hat{\alpha} - C_m)^2 - m^2 V(\hat{\alpha})$.

A few typical plots of this fitted model, with error bars on the estimated midpoint age are shown in Figure 5.5. Initial examination of these errors showed 3 outliers, where the confidence interval was markedly larger than others. Examination of the data for these patients showed in all cases that the highest Camcog score was only just above the midpoint of the scale. These data were therefore removed from further analysis. The boxplot of confidence intervals, without these outliers, is shown in Figure 5.6. The boxplot of the width of the confidence intervals is skewed; this is to be expected, as the width of a confidence interval calculated from normally distributed data is distributed according to the square root of a χ^2 random variable. It is clear that in many cases the confidence interval is extremely small, of the order of 1 year compared with a typical course of the illness of 10 years, and a typical age range of all patients of 40 - 100 years. Where the confidence interval is bigger than this, it is because there are few data points.

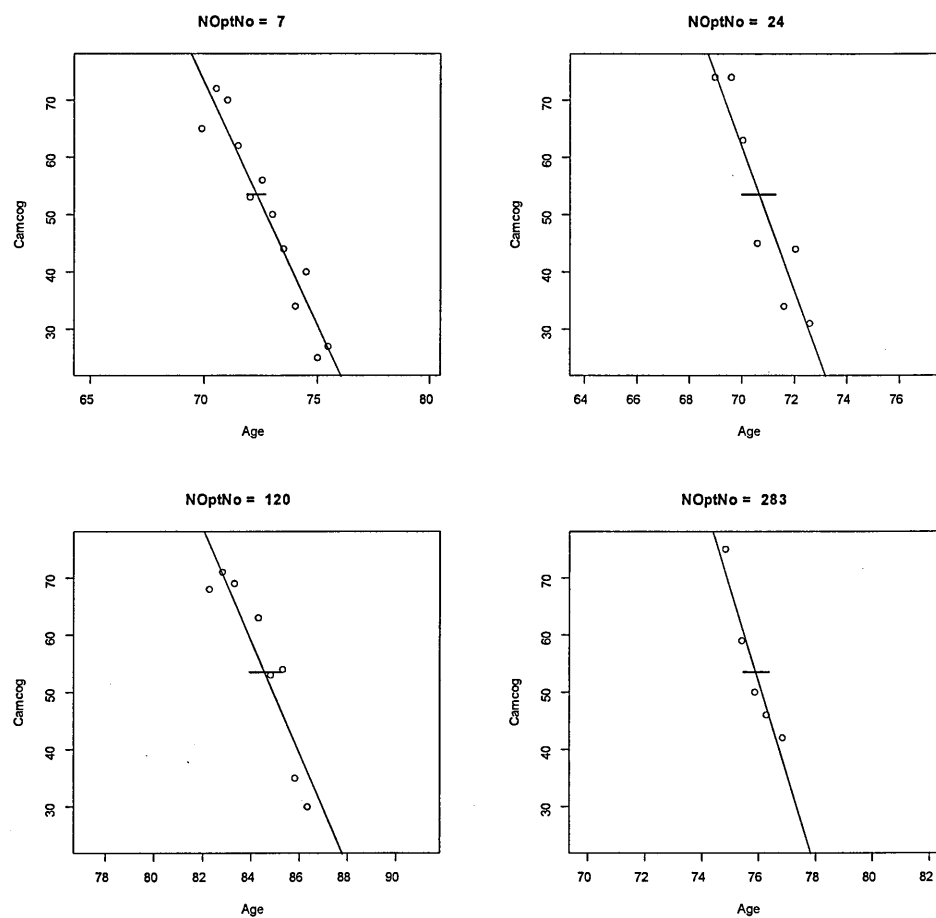


Figure 5.5: Sample linear models from four patients

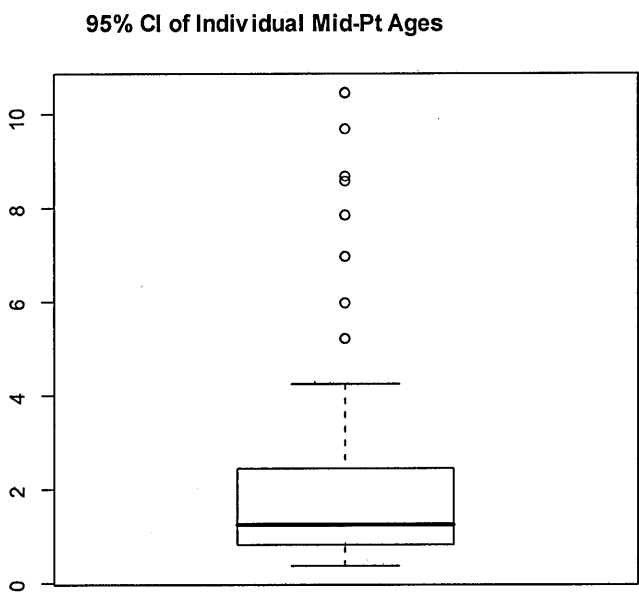


Figure 5.6: Boxplot of Confidence Intervals

Chapter 6

A fixed-effects Model

Once there is a common scale for the age during the course of the decline, it is possible to try and fit all the data points in a common fixed-effects model.

6.1 Theory behind a fixed-effects model using the binomial or logistic curve

The assumption for all patients with a dementing disease is that the patient is “normal” before the onset of the illness: there is a period of decline, and then a period where the score on the cognitive test is around zero. Although controls show a very slight decline of Camcog score with age, it is not marked. Hence the decline looks like Figure 1.1. A function similar to this is the logistic or binomial function

$$\log\left(\frac{y}{1-y}\right) = \alpha + \beta x$$

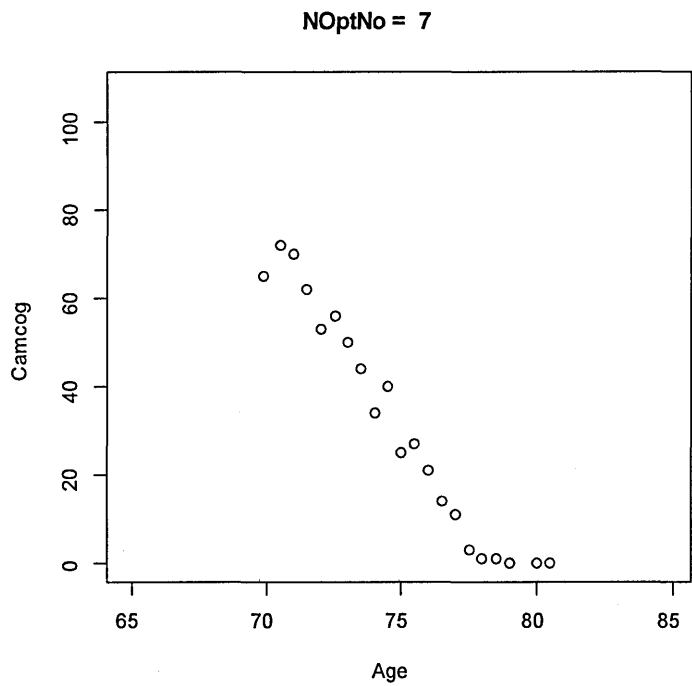
This function is more normally used to model the probability of an event happening or not, but can be used to model the Camcog decline, considering the Camcog score as a proportion of the full-scale score, as long as the assumptions of the model are met. The binomial model is a particular example of a *generalised linear model*. This family of models is used to describe a set of independent random variables y_1, \dots, y_n whose distribution is of the exponential family, the canonical form of which is

$$f(y_i; \theta_i) = \exp(y_i \theta_i - k(\theta_i)) m(y_i)$$

where the θ_i are parameters, m is some function of y_i , and the scale parameter has been set to 1, as is usual for a binomial model. For the generalised linear model there is a smaller set of parameters β_1, \dots, β_p , where $p < n$ and a linear combination of the β_i is some function of $E(Y_i)$. If $\mu_i = E(Y_i)$, then

$$\eta_i = g(\mu_i) = \mathbf{x}_i \boldsymbol{\beta}$$

where \mathbf{x}_i is a $1 \times p$ row vector of explanatory variables, and $\boldsymbol{\beta}$ is a $p \times 1$ column vector of parameters. The function g is the *link function*, and allows different types of model



Complete scores over time

Figure 6.1: Complete Camcog scores over time

to be fitted in the same way, by varying the link function. For the binomial model,

$$g(p) = \log \left(\frac{p}{1 - p} \right)$$

To make things clearer, look at a subset of the data, considering only one patient, and one explanatory variable: the patient’s age at the time the Camcog is completed. A graphical representation of the data is shown in Figure 6.1.

Using the well-known result

$$E \left[\frac{\partial (\log(f(y_i \theta_i)))}{\partial \theta_i} \right] = 0$$
$$\frac{\partial \log(f(y_i \theta_i))}{\partial \theta_i} = y_i - k'(\theta_i)$$
$$\mu_i = E(Y_i) = k'(\theta_i)$$

The canonical link function was used in the analysis, this being $g = k'^{-1}$
The model

$$\log \left(\frac{p_i}{1 - p_i} \right) = x_i \beta_i$$

cannot be fitted with a straightforward linear model, as described above, because one of the main assumptions of that model is that the variance is constant, which is not the case. The data have a binomial distribution, i.e. $Y \sim B(n, p)$, and hence the expectation of Y_i , $E(Y) = np$ and the variance of Y , $V(Y) = np(1 - p)$.

It should be possible to fit a model by iterative weighted least squares, using estimates of p_i to calculate the weights. Consider a function ψ of the i th Camcog score. The best estimate of p_i is the expectation $E\left(\frac{Y_i}{n_i}\right)$. Taylor expansion about p_i gives

$$\psi\left(\frac{Y_i}{n_i}\right) = \psi(p_i) + \psi'(p_i)\left(\frac{Y_i}{n_i} - p_i\right) + \frac{1}{2}\psi''(p_i)\left(\frac{Y_i}{n_i} - p_i\right)^2 + \dots$$

But

$$E\left(\frac{Y_i}{n_i} - p_i\right) = 0$$

and

$$V\left(\frac{Y_i}{n_i}\right) = E\left(\left(\frac{Y_i}{n_i} - p_i\right)^2\right) = \frac{p_i(1 - p_i)}{n_i}$$

so that

$$\begin{aligned} E\left(\psi\left(\frac{Y_i}{n_i}\right)\right) &= \psi(p_i) + \frac{1}{2}\psi''(p_i)\frac{p_i(1 - p_i)}{n_i} + \dots \\ &\simeq \psi(p_i) \end{aligned}$$

$$\begin{aligned} V\left(\psi\left(\frac{Y_i}{n_i}\right)\right) &= V\left(\psi\left(\frac{Y_i}{n_i}\right)\right) + V\left(\psi'(p_i)\left(\frac{Y_i}{n_i} - p_i\right)\right) + \dots \\ &= 0 + (\psi'(p_i))^2 V\left(\frac{Y_i}{n_i}\right) + \dots \\ &= (\psi'(p_i))^2 \left(\frac{p_i(1 - p_i)}{n_i}\right) + \dots \\ &\simeq (\psi'(p_i))^2 \left(\frac{p_i(1 - p_i)}{n_i}\right) \end{aligned}$$

But

$$\psi(p) = \log\left(\frac{p}{1 - p}\right)$$

and differentiating gives

$$\psi'(p) = \frac{1}{p} + \frac{1}{1 - p} = \frac{1}{p(1 - p)}$$

and

$$\begin{aligned} E\left(\log\left(\frac{Y_i}{n_i - Y_i}\right)\right) &\simeq \log\left(\frac{p_i}{1 - p_i}\right) \\ V\left(\log\left(\frac{Y_i}{n_i - Y_i}\right)\right) &\simeq \frac{1}{n_i p_i (1 - p_i)} \end{aligned}$$

The aim is to fit

$$\log\left(\frac{p_i}{1 - p_i}\right) = \mathbf{x}_i \boldsymbol{\beta}_i$$

which means, using

$$z_i = \log\left(\frac{y_i}{n_i - y_i}\right)$$

and therefore minimising

$$\sum_{i=1}^m (z_i - \mathbf{x}_i \boldsymbol{\beta})^2 n_i p_i (1 - p_i)$$

p_i is not known, but an initial estimate of

$$p_i = \frac{y_i}{n_i}$$

and the weights are

$$\frac{y_i(n_i - y_i)}{n_i}$$

These values can be used to calculate $\boldsymbol{\beta}$, and hence a more accurate set of p_i , and an iterative process will soon lead to an acceptable level of accuracy.

6.2 Considering the covariates

The factors I would like to consider as fixed-effects are:

- midpoint age, i.e. the age calculated earlier as the midpoint of the cognitive decline;
- Age at onset – at the first visit to Optima, the partner of the patient is asked for his/her best estimate of the onset of cognitive problems. This is a very subjective measure, probably influenced by later happenings, and requiring the partner to remember and analyse events sometimes several years in the past. It is perforce very imprecise; nonetheless in the absence of a large pre-emptive study, it is the best available measure;
- Gender;
- Homocysteine The blood chemical homocysteine is already known to be associated epidemiologically with the risk of developing both dementia and heart disease. A higher homocysteine level is linked with a higher level of heart disease and of dementia. A higher homocysteine level is associated with a lower intake of vitamin B12;
- APOE4 genotype. The chemicals coded by the APOE genes are known to be involved in the metabolism of homocysteine The APOE gene has 3 alleles: APOE2, APOE3 and APOE4. Patients with 2 copies of the APOE4 allele have a higher risk of developing heart disease and dementia;
- Diagnosis - Alzheimer's disease or other type of dementia;
- Heart arrhythmia;
- Drugs. In recent years drugs have become available to treat the symptoms of Alzheimer's Disease. They have no effect on the underlying disease process, but instead boost the level of a brain chemical (cholinesterase), which is depleted in Alzheimer's patients. Anecdotally, these drugs slow the initial rate of decline, but eventually the patient suffers a much more precipitous decline;

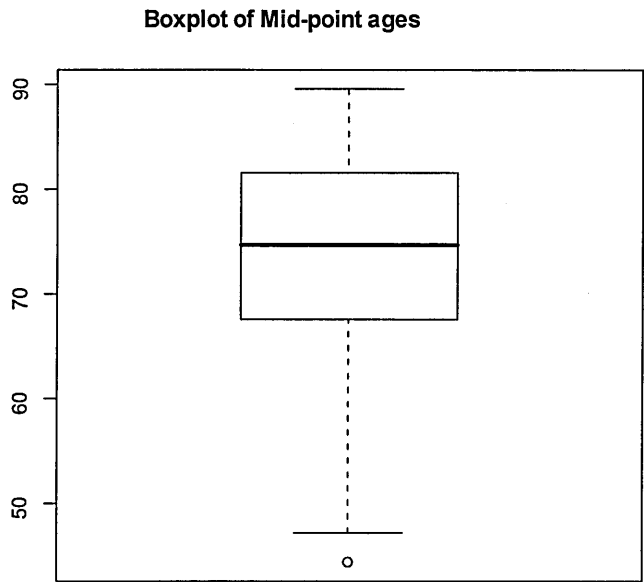


Figure 6.2: Boxplot of Mid-point ages

- Age at first visit;
- Correction to Camcog for first visit. When the person is first seen, it is the first time they are exposed to the Camcog questionnaire. On all subsequent visits, they may have a memory of the questions, and hence have an enhanced score because they had learned some of the answers - this type of correction is commonly called a learning correction. As patients with dementia typically have a poor memory, this factor may not prove to be significant, but it should be included.

Continuous explanatory variables, or some suitable transformation of them, need to be fairly evenly spread out. Let us look at the distribution of each of these factors in turn.

6.2.1 midpoint age

Minimum	44.4
1st quartile	67.6
Median	74.7
Mean	73.9
3rd quartile	81.5
Maximum	89.6

Table 6.1: Summary of midpoint ages

As is to be expected, these data are skewed towards the upper age range – few people develop dementia in their 30s and 40s. The skewness is -0.51. The data need

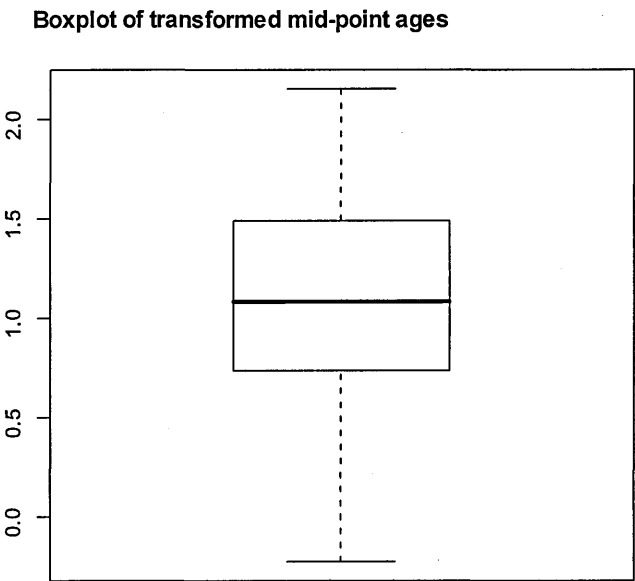


Figure 6.3: Boxplot of transformed mid-point ages

to be transformed so that the older values are compressed, and the younger values stretched. A suitable transformation turns out to be:

$$\ln \left(\frac{MidptAge}{100 - MidptAge} \right)$$

The distribution of the transformed values is shown in Figure 6.3

The transformed data have skewness -0.03 . The transformed data are as unskewed as can be expected. Therefore this transformation will be used in the model.

6.2.2 Age at onset

The Age at onset obviously bears some relationship to the midpoint age, as the illness typically progresses over 5-15 years. Hence the onset of first symptoms is unlikely to be less than 10 years before the midpoint, or more than 1 year before the midpoint. It seems reasonable to consider the difference between the two ages as an independent variable:

$$CorrAgeOnset = AgeOnset - MidpointAge$$

It was not found necessary to transform the corrected age at onset.

6.2.3 Age at episode 1, Correction for episode 1

Patients come to Optima at very different stages in their illness; some come quite early and some when the decline in their cognitive ability is already very apparent to an

outside observer. I therefore included two factors in the model to allow for this. I included a value for the age at episode 1, again taking a corrected value relative to the age at midpoint. I also included a factor which was only included for the first episode, to allow for any learning effect.

6.2.4 Homocysteine (Hcy)

Homocysteine is a chemical found in the blood, and is related to the levels of vitamin B12. The higher the homocysteine, the lower the uptake of B12. It has been found in epidemiological studies to be related to the incidence of dementia, in that people with a high level of homocysteine are more likely to suffer from dementia than those with a low level.

Because levels of homocysteine are known to vary with age, and do show considerable variation over the course of the patient's illness; the only measure used was that taken at the first episode, and these values were classified as "normal", or "high". Homocysteine values above 15 $\mu\text{mol/litre}$ were taken as high[28].

6.2.5 Genotype

There is a gene known as the APOE gene, which is known to affect the way the body processes homocysteine, and is known epidemiologically to influence the prevalence of dementia and cardiovascular disease. The APOE gene has 3 alleles, known as APOE2, APOE3 and APOE4. People with two copies of the APOE4 gene process homocysteine differently. I therefore classified my patients as having the APOE44 allele or not, and I also looked for an interaction between this and homocysteine level.

6.2.6 Diagnosis

Not all Optima patients have Alzheimer's Disease; there are many other, rarer types of dementia which do occur, particularly in younger patients. Because there are so few patients with rarer dementias, I have classified the dementias into those of Alzheimer's type, and others.

6.2.7 Heart arrhythmias

There is some evidence[27] that the brains of some Alzheimer's patients may be short of oxygen because of heart failure. When patients are first examined, a record is made of the steadiness of their heartbeat. In the absence of other measurements, it would be interesting to see if this is a significant covariate. Some people are fitted with pacemakers, and I initially included the presence/absence of a pacemaker as a possible covariate. Unfortunately there are only a very few such people in this study, and one at least is atypical, being much younger than average, and with a diagnosis of "other dementia". Although this is in itself very interesting, it precludes doing an analysis on the significance of pacemakers.

6.2.8 Drugs

The anticholinesterase drugs which have become available recently are reputed to slow or stop the steady decline of cognitive skills, at least for a while[15]. It would be interesting to see if this effect can be detected. Patients on the drugs are again reputed eventually to suffer a much more catastrophic decline after a few years, but there are not enough data in the Optima study to see this effect, as the drugs had not been available long enough for this effect to be observable.

6.3 Fitting the model

I used the glm model[14][69] from R, to model the cognitive decline as a logistic curve, just as already used for individual patients. I used the entire data set, and included various factors as covariates within the model. There are many possible covariates, and I found it necessary to run many versions of the model, with differing sets of covariates, to find the eventual best model. To avoid over-parameterising the model, I only included interactions between covariates if I had some reason to suspect an interaction existed, and where it might be possible to interpret the results. I used the R functions add1 and drop1 to see the effect of dropping single factors, and looked at model diagnostics, and the deviance residuals to check which was the best model:

Consider two models:

model 1 has residual deviance $RD1$ on $DF1$ degrees of freedom,

model 2 has residual deviance $RD2$ on $DF2$ degrees of freedom, where model 1 has fewer covariates and so $DF2 > DF1$.

A p -value for a test of the null hypothesis that the omitted covariates are significant is obtained by using the result that $RD2 - RD1$ has an approximate chi-squared distribution with $DF2 - DF1$ degrees of freedom.

The model that eventually emerged as the best had the following covariates:

- midpoint age;
- Adjusted age at episode 1, Correction for episode 1;
- First episode;
- Anti-cholinesterase drugs;
- Initial homocysteine level;
- APOE genotype;
- Initial homocysteine level interacting with APOE genotype;
- Gender interacting with midpoint age.

The other covariates were not found to have a significant effect.

A table of the results of the final model is shown below:

	Estimate	Std Error	z value	Pr(> z)	
AdjAge	-0.490	0.031	-12.49	< 2e-16	***
midpoint age	0.165	0.0052	-94.90	1.16e-14	***
Age at onset	0.006	0.0021	7.72	0.014	*
Age first seen	0.029	0.0057	4.99	5.98E-e-07	***
Drugs yes	0.28	0.028	10.14	< 2e-16	***
Gender M	-0.016	0.036	-0.45	0.65	
Hcy normal	0.215	0.016	13.23	< 2e-16	***
APOE 44	0.242	0.029	8.33	< 2e-16	***
First visit	0.162	0.023	6.95	3.6e-12	***
Hcy N:APOE 44	-0.211	0.049	-4.34	1.2e-05	***
GenderM:midpoint age	-0.069	0.031	-2.24	0.025	*

Table 6.2: Results of the fixed effects model

The original model included 973 data points. When I looked at the Cook’s distances for this model, one point had an extremely large Cook’s distance (see Figure 6.4). When I reran the model without this point, the model was not significantly different, but the Cook’s plot showed no other single points with such high influence. Consequently all the other models have been run without this point. Diagnostic plots for this model are shown in Figures 6.5 and 6.6. Note the initially somewhat puzzling line of points at the bottom left of the plot of fitted values against residuals (Figure 6.5): these points are those where the Camcog score is zero. Such an appearance is typical of the type of model; a binary regression (i.e. 0/1 response) would show two roughly parallel lines of points, and this kind of diagnostic plot would then have no meaning. [12]. The qq plot (Figure 6.6) should approximate to a straight line.

6.4 Effect of a lower initial Camcog

The mean Camcog score of the Optima controls is 97. I therefore reran the fixed-effects model using this as the initial Camcog score, rather than the full-scale value of 107. The result was a very slight change in the parameters of the order of a few percent. A comparison of the models is shown graphically in Figure 6.7, and numerically in Table 6.3.

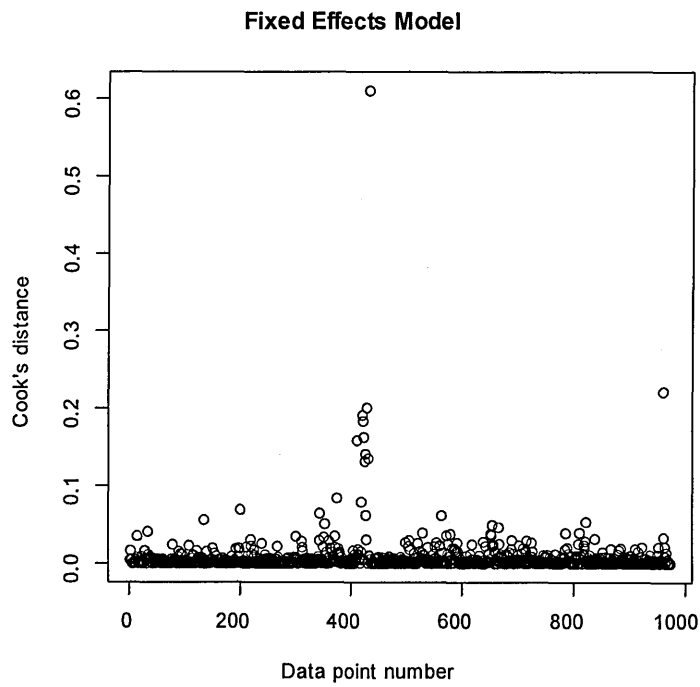


Figure 6.4: Cooks distances showing the influential point

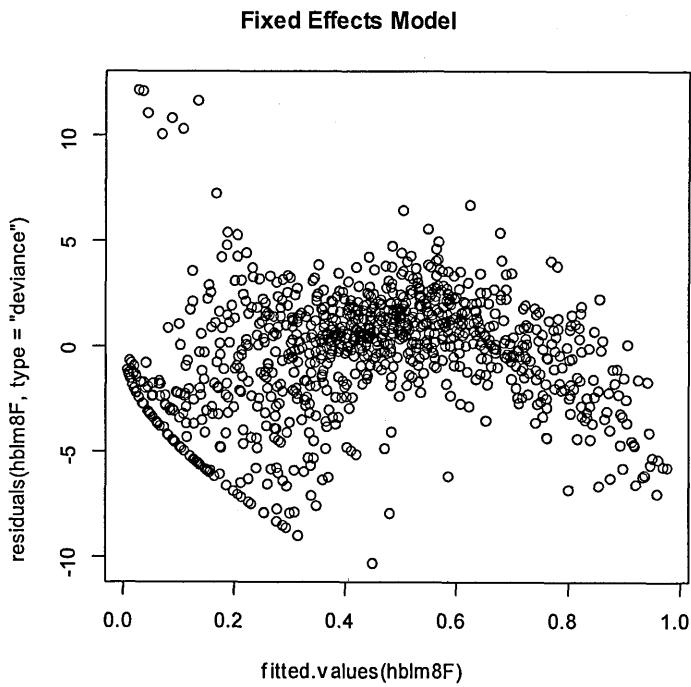


Figure 6.5: Residuals vs Fitted values for fixed effects model

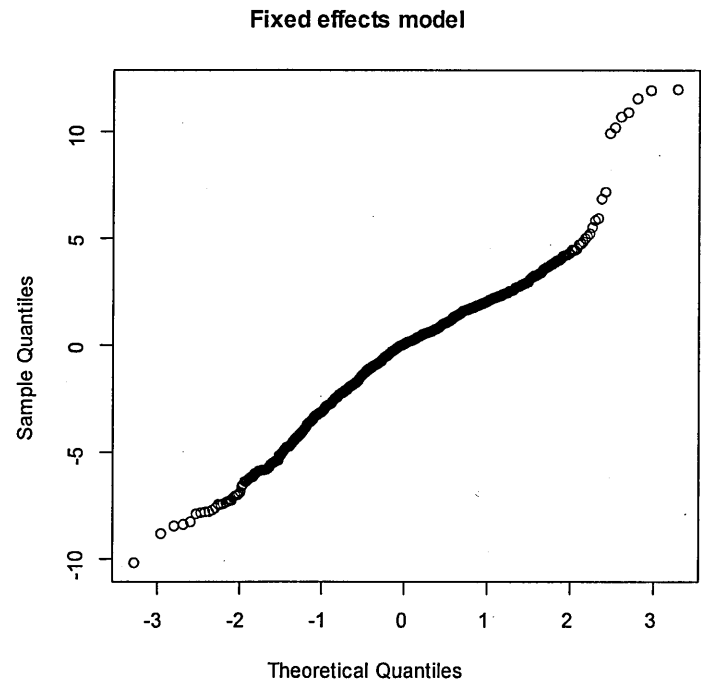


Figure 6.6: Diagnostic plots for the final fixed effects model

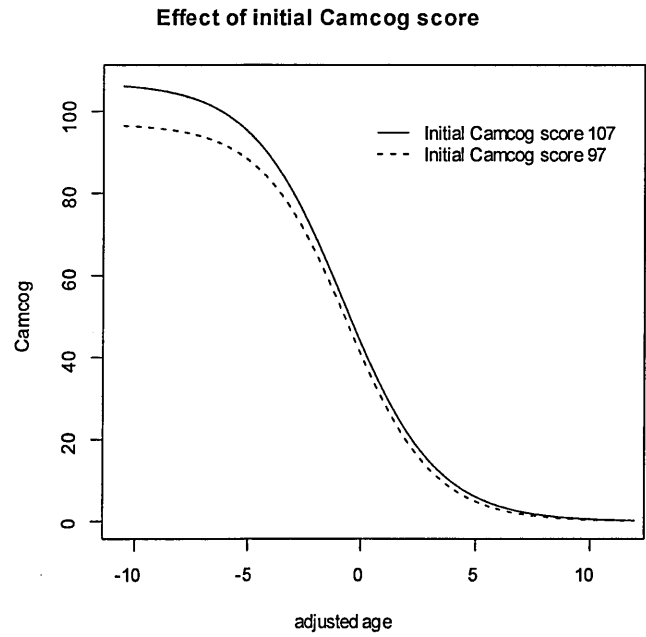


Figure 6.7: Comparison of models with differing initial Camcog scores

	Initial Camcog 107	Initial Camcog 97
Intercept	-0.385	-0.329
Adjusted age	-0.490	-0.525
Midpoint age	0.165	0.117
Age at onset	0.00605	0.00723
Age of first visit	0.0285	0.038
First visit	0.162	0.163
Gender M	-0.0161	-0.085
Normal Hcy	0.215	0.225
APOE4	0.243	0.207
Drugs	0.278	0.323
Normal Hcy:APOE4	-0.211	-0.119

Table 6.3: Comparison of models with differing initial Camcog scores

Chapter 7

Random-effects models

As explained in section 7.1, a random-effects model uses all the data, but grouped by individual Optima ID. The packages allow for random effects to be applied to individuals, but nevertheless check whether there is any pattern within the data, showing fixed effects of the various covariates.

I have used two software packages to model random effects: `glmmPQL`[70] and `nlme`[38][31]; both of these run within R.

7.1 Theory behind the random-effects models

I have already described using a linear equation to model the middle part of the curve for each individual patient. A similar process can be used to model the whole curve for each patient: a non-linear random-effects model. I need a non-linear equation to model the curve, and a logistic regression provides the correct shape.

$$Y = \log\left(\frac{C}{107 - C}\right) = \mathbf{X}\boldsymbol{\beta} + \epsilon$$

For the individual patient i

$$Y_i = \mathbf{X}_i\boldsymbol{\beta} + \epsilon_i$$

The random-effects model is

$$Y_i = \mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\mathbf{b} + \epsilon_i$$

where \mathbf{b} is the unknown vector of random effects such that

$$\mathbf{b} \sim N(\mathbf{0}, \boldsymbol{\Sigma}_b)$$

i.e. \mathbf{b} is normally distributed with mean vector 0 and variance/covariance matrix $\boldsymbol{\Sigma}_b$.

The columns of \mathbf{Z} are a subset of \mathbf{X} , i.e. values of a subset of the explanatory variables, acting on each patient separately.

ϵ is the vector of residuals and is generally of the form $\epsilon \sim N(\mathbf{0}, \sigma^2\mathbf{I})$.

Random effects \mathbf{b}_i and residuals ϵ_i are assumed to be independent.

Two R functions are available for fitting these models.

- The function `nlme` uses the restricted maximum likelihood (REML) to calculate the maximum likelihood;
- the function `glmmPQL` uses Penalized Quasi-Likelihood.

7.2 Modelling random effects with `glmmPQL`

The `glmmPQL` function can be used in a very similar way to the generalised linear model function, `glm`, using the same data set and the same formula definition. I used this function because it can be used to fit the exact model I have already used for individuals. However, as the function calculates several parameters for each individual, and then looks for fixed effects within these parameters, it can only be used for those individuals with a sufficient number of data points, so that over-parameterisation does not occur. In fact, to give less random variation I only included individuals with at least seven data points, to reduce the errors on the individual parameters. There are 58 such people within the dataset, comprising 671 of the 972 total data points available.

I specified that the model should fit a within-group random effect on the intercept.

7.2.1 Results of fitting the data with `glmmPQL`

The fitted model had an intercept of -0.505 ± 0.145 , and the random effect within groups had a value of 0.200. Hence it can be seen that the random variation from one individual to another is actually not very large in comparison with other effects. Diagnostics for this fit are shown in Figures 7.2 and 7.1. The Shapiro-Wilk statistic [56] for the qq plot is $W = 0.9455$.

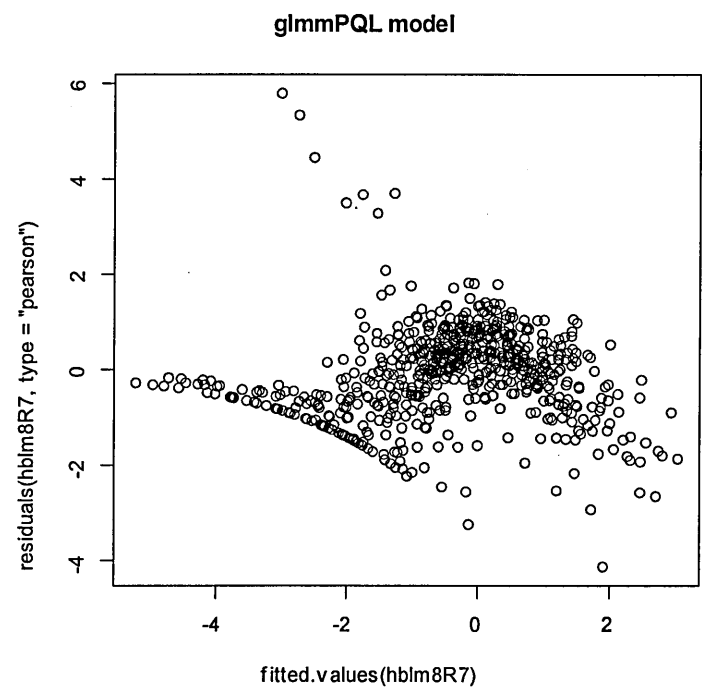


Figure 7.1: Residuals vs Fitted values for glmmPQL model

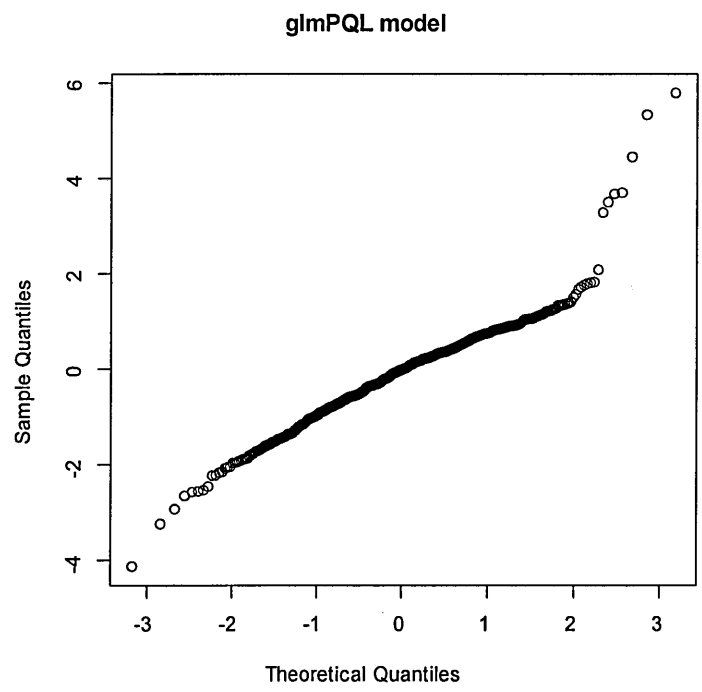


Figure 7.2: Diagnostics for the final random effects model

7.2.2 Fixed effects with glmmPQL

I looked for fixed effects on the variables which had already been observed to be significant in the fixed-effects model described in chapter 6. Some effects were not longer significant in this random-effects model: the covariates which were significant are shown in table 7.1.

	Value	p-value
midpoint age	0.242	0.0247
Normal Hcy	0.312	0.0006
APOE	0.442	0.0053
Hcy*APOE	-0.449	0.0729
Drugs	0.417	0.0002

Table 7.1: Significant covariates from glmmPQL model

The significance of the values of these covariates will be discussed further in chapter 9.

7.2.3 Comparison with fixed-effects model

The values given to the effects of the covariates with the glmmPQL random-effects model and the fixed-effects model discussed earlier are very similar. A comparison of the models is shown graphically in Figure 7.3, and numerically in Table 7.2.

Note that the models run on different data sets: the fixed-effects model includes individuals where there are only a few data points.

7.3 Modelling random effects with nlme

Recently Optima has been working with people who do not have a diagnosis of dementia, but instead are classified as MCI (Mild Cognitive Impairment).

Such people were originally assumed to be in the early stages of dementia, and indeed some people proceed to develop dementia, but further study has shown that some people with MCI can revert to cognitive normality, and some people switch between MCI and normal more than once. This work is quite new, and we have not yet had the

	random-effects model		fixed-effects model	
	parameter	p-value	parameter	p-value
midpoint age	0.24	0.0006	0.17	< 2e-16
Age onset	0.0057	0.69	0.0061	0.014
Age at first visit	0.043	0.13	0.029	5e-07
First visit	-0.041	0.66	0.16	3e-12
Gender M	0.028	0.88	-0.16	0.65
Normal Hcy	0.31	0.0006	0.21	2e-16
APOE4	0.44	0.0053	0.25	2e-16
Drugs	0.42	0.0002	0.28	2e-16
Normal Hcy:APOE4	-0.45	0.073	-0.21	4e-05
midpoint age:Gender	-0.10	0.56	-0.069	0.025

Table 7.2: Comparison of fixed effects and random effects models

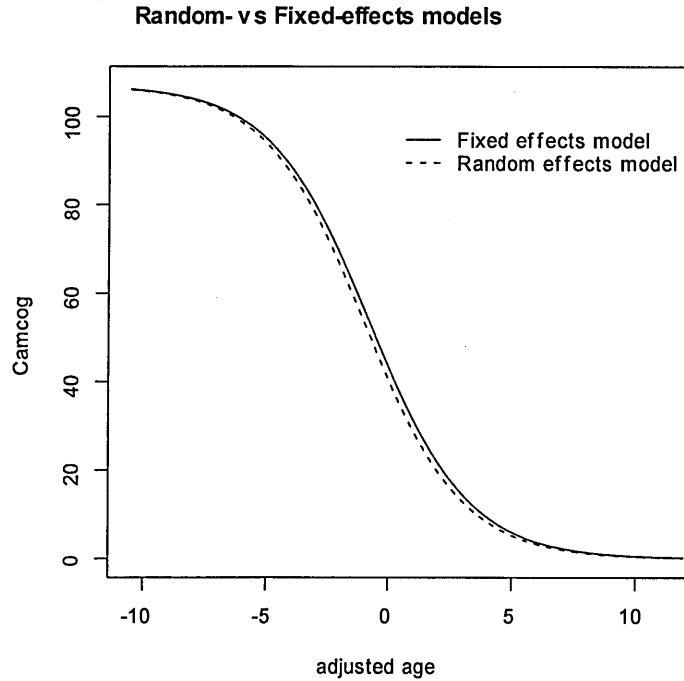


Figure 7.3: Comparison of fixed and random effects models

opportunity to see if everyone who at one stage had a diagnosis of MCI will eventually develop dementia. However, it does raise the interesting possibility that some of the Optima patients with dementia may not in fact have started their illness at a Camcog score close to full-scale, but instead had hovered for some time at a lower Camcog value.

I chose to use the three-parameter logistic function, which gives the same inverse S-shaped curve I have used in the previous chapter[32]. The major difference between this model and the previous two-parameter model is that this also allows the asymptote of the curve to vary from individual to individual. I therefore used the three-parameter model to estimate this asymptote. A model of the decline, with the significance of the three parameters is shown in Figure 7.4. Note that this model will always have the parameter $scal < 0$. The function modelled is

$$Camcog = \frac{Asym}{1 + \exp\left(\frac{x_{mid-age}}{scal}\right)}$$

For the initial model, I allowed a random effect on all three parameters, $Asym$, x_{mid} and $scale$. This function can only be used to model the decline where there at least 4 measurements of a patient's cognitive abilities, and I also had to remove all measurements where the Camcog score was zero in order to get the model to converge. Even so the model did not converge, until I removed the data for one patient who showed an exceptionally slow decline compared with most other patients. I used 520 data points from 53 individuals.

With these limitations, the model converged, and produced data on the random

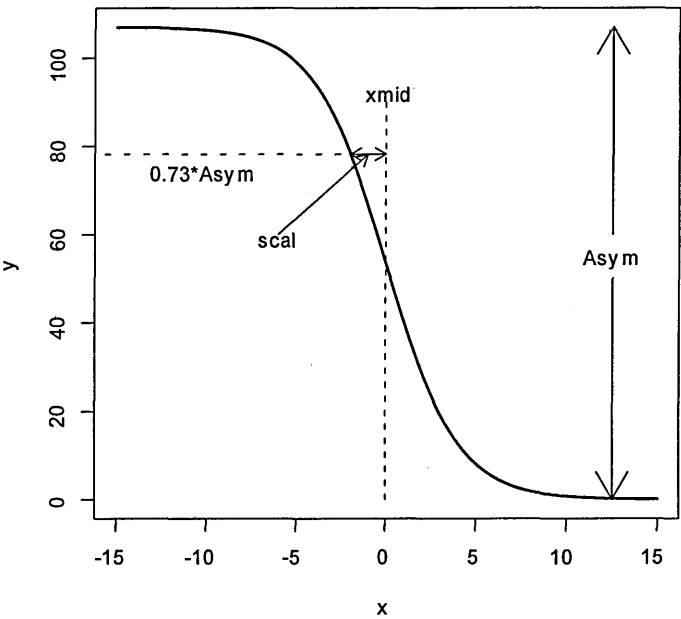


Figure 7.4: Theoretical model of 3-parameter nlme

	AIC	BIC	Loglik
Asym+xmid+scal	-1428	-1385	724
Asym+xmid	-1283	-1253	648
Asym+scal	-1370	-1340	692
xmid+scal	-1416	-1386	715

Table 7.3: Comparison of nlme models with varying random effects

effects on all three parameters. The pairs plot of the ensuing model (Figure 7.5) indicates that there is a strong correlation between the random effects on xmid and scale, suggesting perhaps that one of these random effects can be dropped. Although I ran models with random effects on Asym and xmid, on Asym and scal, and on xmid and scal, the results show clearly that the model with random effects on all three parameters is the best (see Table 7.3).

The diagnostics for the model with no covariates but random effects on all three parameters are shown in Figures 7.6 and 7.7.

Although I would have liked to use the model to look at all the covariates, when I ran nlme with random effects on three parameters and fixed effects on all the covariates, the model did not converge. Instead I looked at the more significant covariates from the fixed-effects model, and from glmmPQL, and ran the model with a subset of covariates. The covariates I used were

- Homocysteine
- APOE allele

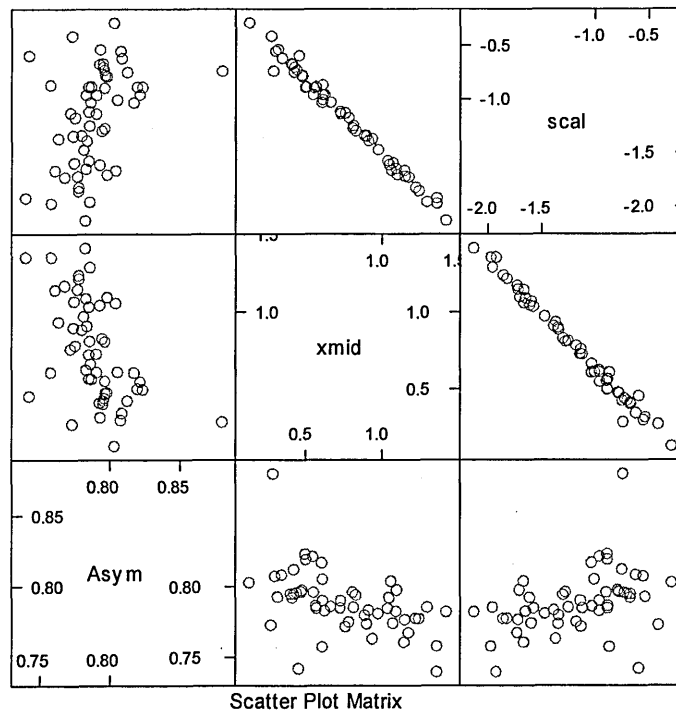


Figure 7.5: Pairs plot from the nlme model

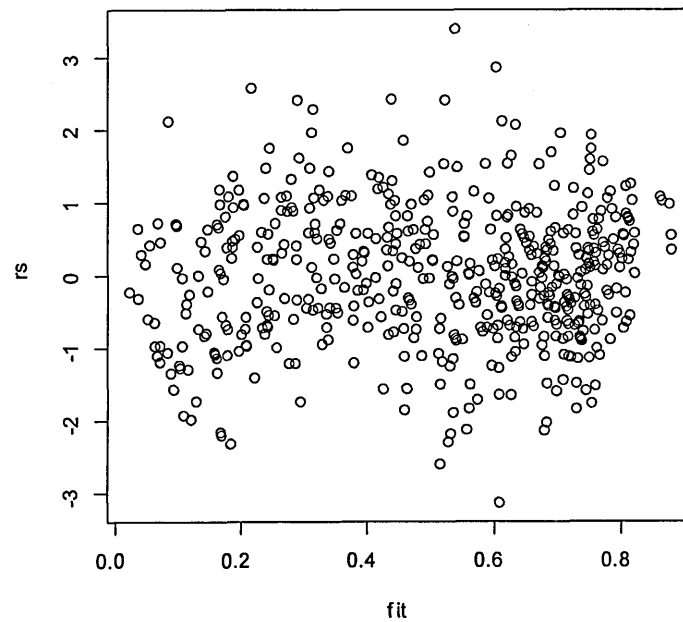


Figure 7.6: Plot of fitted values vs residuals for nlme

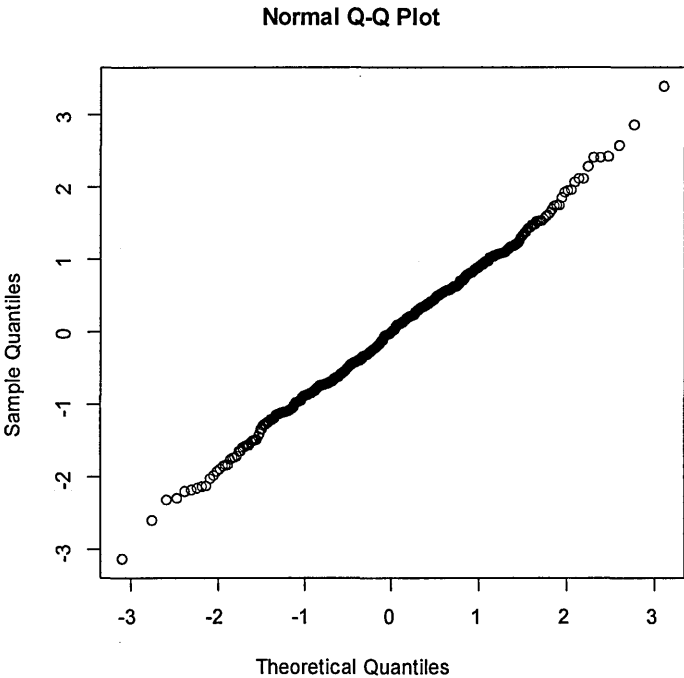


Figure 7.7: Diagnostics for nlme model with random effects on all parameters

	Value	SD of random effect
Asym	0.789	0.033
xmid	0.752	0.346
scal	-1.170	0.486

Table 7.4: Parameters calculated by nlme

- Anti-cholinesterase drugs
- Age at midpoint

This model was not significantly better than the model with no covariates (p-value of 0.76).

The values calculated by this model for the various parameters and graphs of the varying parameters are shown in Figures 7.10 to 7.4

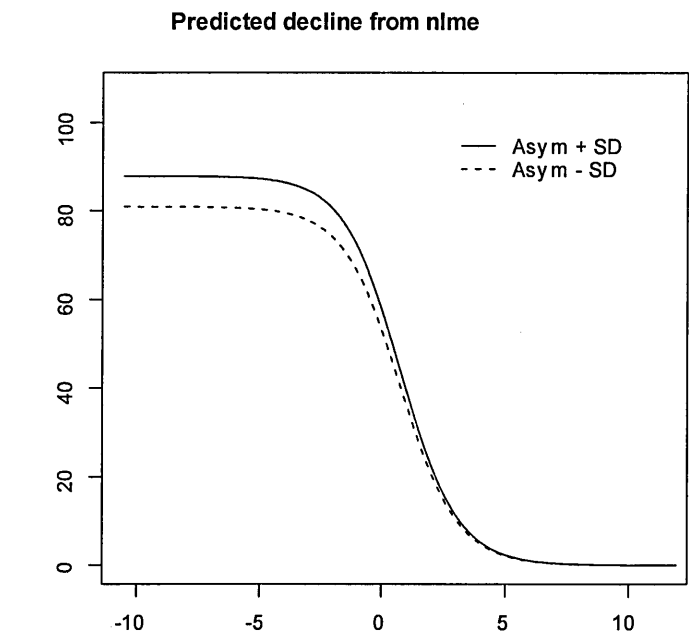


Figure 7.8: Predicted decline from nlme at limits of Asym

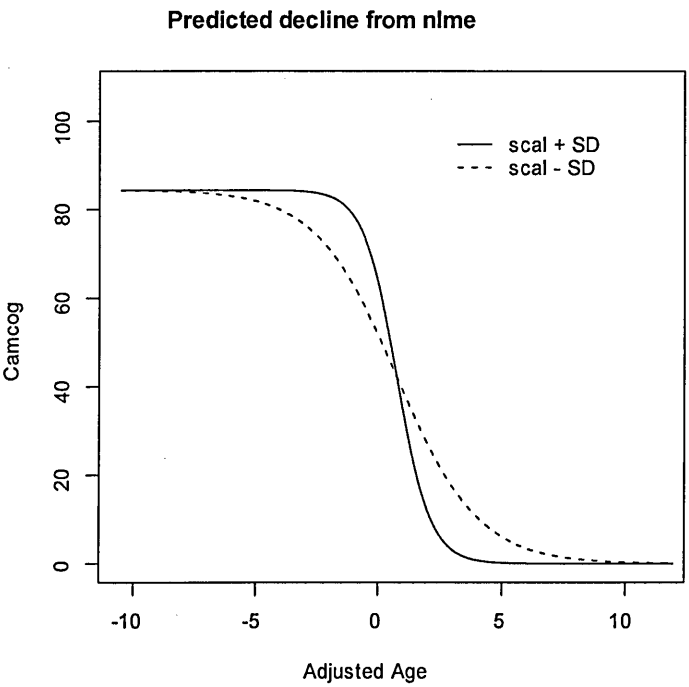


Figure 7.9: Predicted decline from nlme at limits of scal

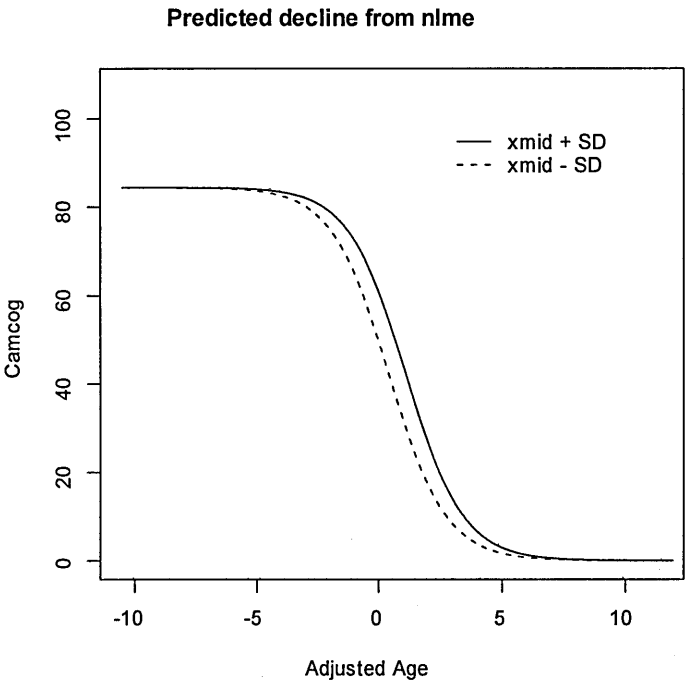


Figure 7.10: Predicted decline from nlme at limits of xmid

Chapter 8

Comparing the models

The models I have used in this dissertation are:

- generalised logistics model using the binomial function;
- linear model to calculate midpoint age for each individual;
- fixed-effects model to develop a possible model of the decline and the effects of covariates on the rate of decline;
- random-effects model using glmmPQL to confirm the results of the fixed-effects model in a theoretically more applicable fashion;
- random-effects model using nlme to see if the initial Camcog score is likely to vary much from full-scale.

The binomial function was used to model the Camcog score separately for each individual. The model apparently gave a good fit to the data for all individuals, and the diagnostics indicated that this was a valid approach. Fitting a model to each patient individually does not allow any inference to be made about covariates, but does give confidence that the model is a reasonable one to use.

A linear least-squares model is used to fit the central part of the decline. The results show that in the central part of the Camcog scale (20-80 points) this model fits the data well, giving a small standard deviation for the age at midpoint for all individuals. A boxplot of Standard Deviations was shown earlier (Figure 5.6), but is repeated here for convenience - Figure 8.1.

This shows that the midpoint age estimated from the linear model has a fair accuracy, and can be used to fit a single model to all the data; using the covariates to account for the individual difference between patients, and ignoring for the time being any effect that is purely random. The diagnostics for this model show that this is a reasonable assumption, and the smaller error on the parameters calculated for the covariates allows many different models to be tested, to find the best combination of influential covariates, and not overparameterise the final model. A sample of the model testing is shown in appendix A.

Although it appears in this case that the random variation between patients is small compared with the effect of the covariates, the fixed-effects model is not theoretically

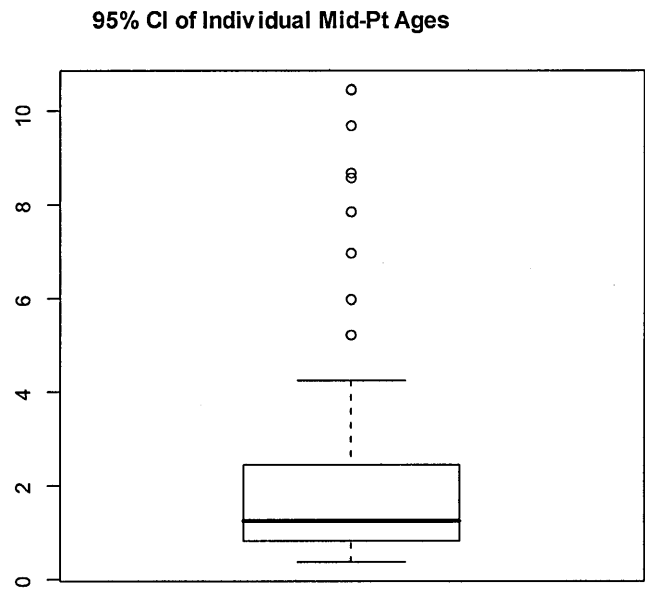


Figure 8.1: 95 percent CI of errors on mid-point ages

a good one to use. It is more appropriate to allow a random effect on the midpoint age and on the slope. The theory behind the random-effects models is explained in section 7.1 above. While the theory is common for the two models I have used, the computer implementation is different. The linear model and the generalised linear model both work by maximising the likelihood function: for the random-effects models this is not possible, as there is no functional calculation for the likelihood. The two models maximise an approximation to the likelihood function. `glmmPQL` maximises the Penalized Quasi-Likelihood, and `nlme` the restricted maximum likelihood.

All random-effects models suffer from problems of convergence, and indeed I had to drop some data points to get both models to converge. `glmmPQL` would not converge unless I dropped the patients with the smallest rate of decline, and `nlme` would not converge if I included any of the points where *Camcog* = 0.

The `glmmPQL` model which gave the best fit to the data estimated a parameter for the intercept for each individual, as well as estimates of the parameters of the various covariates. My initial model had a random effect on the slope and intercept, but I could drop the random effect on the slope, and still achieve a good fit to the data. The extra level of parameterisation compared with the fixed-effects model gave significantly larger errors on the parameters. A table of the parameters and p-values for the various covariates from the fixed-effects and random-effects model using `glmmPQL` is shown in Table 8.1. As can be clearly seen, the p-values from the random-effects model are larger than those from the random-effects model. The values of the various parameters are reasonably close.

	random-effects model		fixed-effects model	
	parameter	p-value	parameter	p-value
midpoint age	0.24	0.0006	0.17	< 2e-16
Age onset	0.0057	0.69	0.0061	0.014
Age at first visit	0.043	0.13	0.029	5e-07
First visit	-0.041	0.66	0.16	3e-12
Gender M	0.028	0.88	-0.16	0.65
Normal Hcy	0.31	0.0006	0.21	2e-16
APOE4	0.44	0.0053	0.25	2e-16
Drugs	0.42	0.0002	0.28	2e-16
Normal Hcy:APOE4	-0.45	0.073	-0.21	4e-05
midpoint age:Gender	-0.10	0.56	-0.069	0.025

Table 8.1: Parameters and p-values from fixed- and random-effects models

The nlme model I used differed from the glmmPQL and fixed-effects model, in that I included an extra parameter giving the asymptote for each individual. This extra parameter is the initial Camcog score for each patient, and I included it to see if there was any significant variation from the standard value of 107 that I used in the other models. I initially allowed a random effect on each of the three parameters (intercept, asymptote and slope) for each individual, as well as the parameters for the various covariates. I hoped to be able to drop some of these random effects, as I could with the glmmPQL model, but unfortunately the fit without these parameters was significantly worse. The nlme model did not give me any meaningful estimates of the parameters for the various covariates, doubtless because of the extra level of parameterisation. This was very disappointing, but not surprising, especially since I had to drop a number of data points in order to get the model to converge at all.

Chapter 9

Interpreting the results

As discussed in chapter 2, earlier research has compared rates of decline in varying groups of people, and sometimes come to the conclusion that decline is faster or slower in a particular group. The model I have used allows a more quantitative approach. The model is

$$\log\left(\frac{C}{107-C}\right) = a - bt + b_1V_1 + b_2V_2 + \dots + b_nV_n$$

where V_1, \dots, V_n are the covariates, The value b gives a measure of how someone's log(cognitive score) will change in the future. Rewriting this gives

$$C = 107 \left(\frac{Ae^{-bt}}{1 + Ae^{-bt}} \right)$$

where $A = e^{(\alpha + \sum b_n V_n)}$. Differentiating C with respect to time, to find the rate of decline, gives

$$\begin{aligned} \frac{dC}{dt} &= 107 \left(\frac{-bAe^{-bt}(1 + Ae^{-bt}) + bA^2e^{-2bt}}{(1 + Ae^{-bt})^2} \right) \\ \frac{dC}{dt} &= \frac{-bAe^{-bt}}{(1 + Ae^{-bt})^2} \end{aligned}$$

As $A = e^{(\alpha + \sum b_n V_n)}$, the rate of decline is critically dependent on the parameters b_n of the covariates. What does this mean in practice? Consider a patient for whom all the covariates are 0, with a Camcog score of 106 at $t = 0$. Calculate the value of a from these initial values:

$$a = \log(106/1) = 4.66$$

Using a value of b of -0.5 (an approximate value from the fixed-effects model), consider the same patient after 1 year. His score then is

$$\log\left(\frac{C}{107-C}\right) = 4.66 - 0.5 = 4.16$$

Hence after 1 year his score will be

$$C = 105.35$$

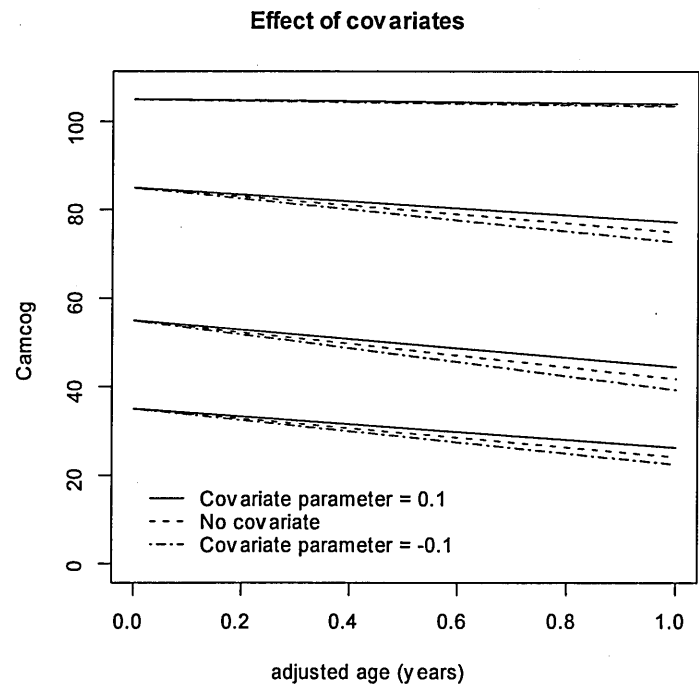


Figure 9.1: Effect of changing the model parameters

By the same calculation, a patient with a starting score of 53 would have a score of 39.50 one year later.

For a similar patient who differs from the first only in the value of the covariate V_n with parameter b_n , the rate of decline from the same starting values is shown in Figure 9.1 for values of b_n of 0.1 and -0.1 .

Starting Camcog	Camcog 1 year later		
	$b_n = 0.1$	no covariate	$b_n = -0.1$
105	104.0	103.7	103.4
85	77.2	75.0	72.7
55	44.4	41.8	39.3
35	26.3	24.2	22.5

Table 9.1: Comparison of change in Camcog for differing covariates

While the actual decline in a year depends on the starting value, it is clear that the more negative b is, the worse the overall decline, and in the middle of the scale, the change in the final Camcog scores is very marked. A patient with an initial Camcog of 85, which is just above the score of 80 where dementia is normally diagnosed, could have declined to a Camcog of 77 - still around initial diagnosis levels, or to a Camcog of 72, at which the dementia is likely to be very noticeable. A person with a Camcog of 55 is likely still to be living at home, although dependent on help for some things. After 1 year, this person may have declined to a score of 44, and is probably still at home with more help, or have declined to a score of 39, and probably living in a nursing home. Since I am modelling cognitive decline, and since the minus sign is inherently

confusing, I will define an **impairment ratio**, which is $\exp(-b_n)$.

The impairment ratio gives a way of comparing the changes in two patients who are otherwise similar, but differ in only one covariate. If patient *A* has covariate $V_n = 1$, and patient *B* has covariate $V_n = 0$, then over a particular time period (e.g. 1 year), if patient *A*'s impairment index ($=\frac{Camcog}{107-Camcog}$) is I_A , patient *B*'s impairment index will be $I_A * \text{impairment ratio}$. If the impairment ratio for a given covariate is 1, the two patients will have similar final scores given the same starting conditions. If the impairment ratio is < 1 the patient with the covariate will have a higher score (i.e. the covariate is protective). If the impairment ratio is > 1 , the patient with the covariate will have a lower score, i.e. the covariate is destructive.

All the covariates are measured relative to a patient who has a midpoint age of 50 years, an initially high homocysteine level, no APOE4 alleles, and does not use anti-cholinesterase drugs.

Let us consider the covariate DrugsA, which is 1 for patients who use anticholinesterase drugs in the early stages of their illness, and 0 for patients who do not use these drugs. The model gives the parameter for this covariate as 0.417, and this gives an impairment ratio of 0.66 This means that over the course of a specific time period, patients who use these drugs will decline at approximately 2/3 the rate of people who do not, all other factors being equal

The model I have used to model the Camcog decline is more normally used to model the probability of an event happening, when the equivalent parameter gives an estimate of how the odds ratio of an event happening will vary with a particular covariate. So in some ways the difference in impairment ratios is similar to the odds ratio.

Interpreting other covariates

Age

age at midpoint	impairment ratio
40	1.10
60	0.91
70	0.81
80	0.68

Table 9.2: Effect of age on impairment ratio

The age I have used in my model is the midpoint age; that age at which I estimate the patient would have had a Camcog score of 53.5, the midpoint of the Camcog scale. The value of the parameter for this variable is 0.24, and the impairment ratios for varying ages are shown in Table 9.2. This shows that the illness progresses faster in young people, and that the difference between someone who is 40 at midpoint age and someone who is 80 is as marked as the difference between someone who does not use anticholinesterase drugs and someone who does.

Age at Onset, Age at Episode 1, First Episode, Gender

None of these covariates is found to have a significant effect on the rate of decline.

Heart arrhythmia, Pacemaker fitted

Initially these covariates seemed to have an effect on the rate of decline. However, a closer examination of the data revealed only two patients with a fitted pacemaker, one of whom was exceptionally young, and only four patients with atrial fibrillation. It was felt that there was insufficient data to analyse.

Diagnosis

The criteria for diagnosis, particularly of the less common illnesses, have changed over the years since Optima started. Currently the illnesses are diagnosed as Alzheimer’s disease, or "other dementias". There is an ongoing process to revisit all patient diagnoses, to provide more detail, and to standardise the diagnostic criteria. I decided to delay looking at the effect of diagnosis until the new data were available.

Homocysteine and the APOE gene

	Impairment ratio
Normal homocysteine not APOE44	0.72
Normal homocysteine APOE44	1.31
High homocysteine APOE44	0.64

Table 9.3: Interaction of Homocysteine and APOE impairment ratios

As already mentioned, homocysteine is a blood chemical that is known to have an epidemiological effect on the prevalence of Alzheimer’s disease, and also incidentally heart disease and stroke. A high level of homocysteine is associated with a higher incidence of heart disease, stroke and Alzheimer’s disease. The way homocysteine is processed by the body is determined by a gene called the APOE gene. Hence there may be an interaction between the APOE gene and homocysteine, and that is what my model shows. The table below shows the three impairment ratios for normal and high homocysteine for APOE44 and other APOE alleles, all relative to a patient with high homocysteine and no APOE44 alleles. It can be seen from Table 9.3 that there is a clear difference: for people without the APOE44 allele, an initially normal level of homocysteine is protective; people with a high level are likely to decline more in a given time period. But for those with the APOE44 allele, the picture is not so clear. Although the APOE44 carriers with a normal level of homocysteine have an impairment ratio of 1.31 (i.e. this is a destructive combination), in fact the errors on the impairment ratio include the value 1, so within a 95% confidence level there is no evidence for any effect on the impairment ratio. There is some evidence that APOE44 carriers with an initially high homocysteine have an impairment ratio < 1, indicating that this combination may be protective.

Chapter 10

Adjusting Camcog values

For the purpose of displaying the fit, the raw data were adjusted to allow for the effect of the covariates. The actual Camcog score at any age can be adjusted according to the actual covariates, using the coefficients given by the model. I applied this adjustment to all the data points available, not just those used in the analysis.

If this is done, the actual score is adjusted, typically by ± 10 Camcog points. A graph of the predicted line of the model and raw data points is shown in Figure 10.1 and also one with model and adjusted data points in Figure 10.3.

The principal corrective covariates are initial homocysteine level, APOE genotype, use of anticholinesterase drugs and midpoint age. The first three of these are available at the first visit, and the midpoint age bears a close relationship to the current age. Hence it may be possible to give some prediction at an initial visit, or soon afterwards, of the likely rate of progression of the illness for any give individual.

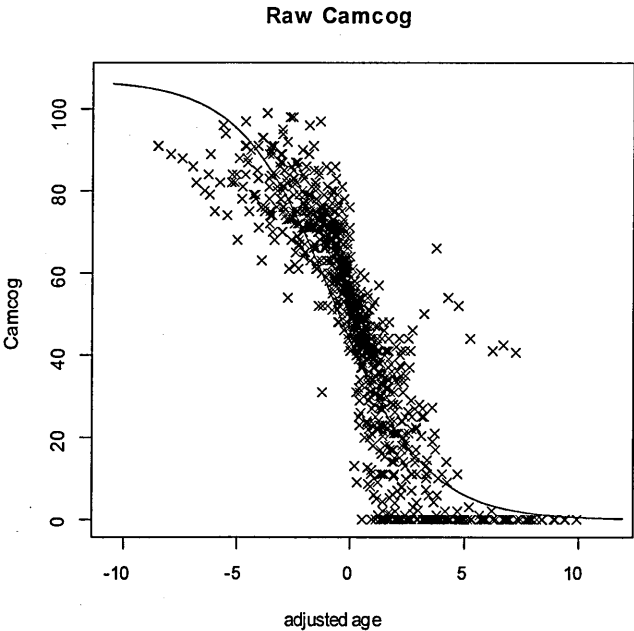


Figure 10.1: Final model and raw Camcog points

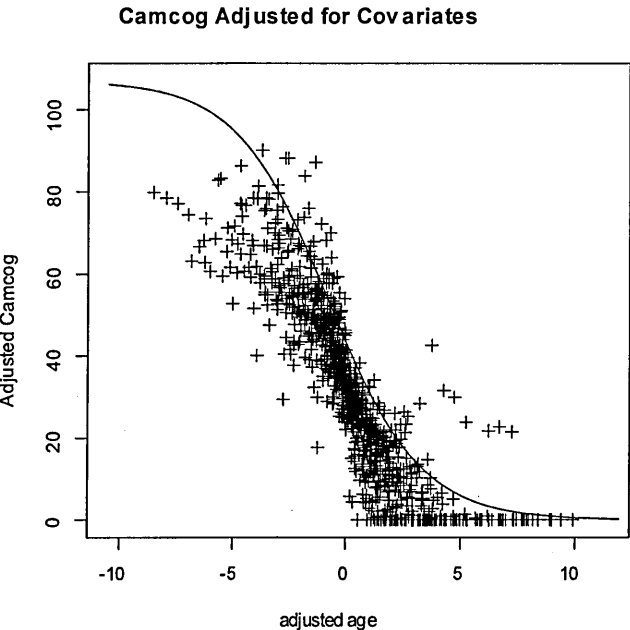


Figure 10.2: Final model and adjusted Camcog points

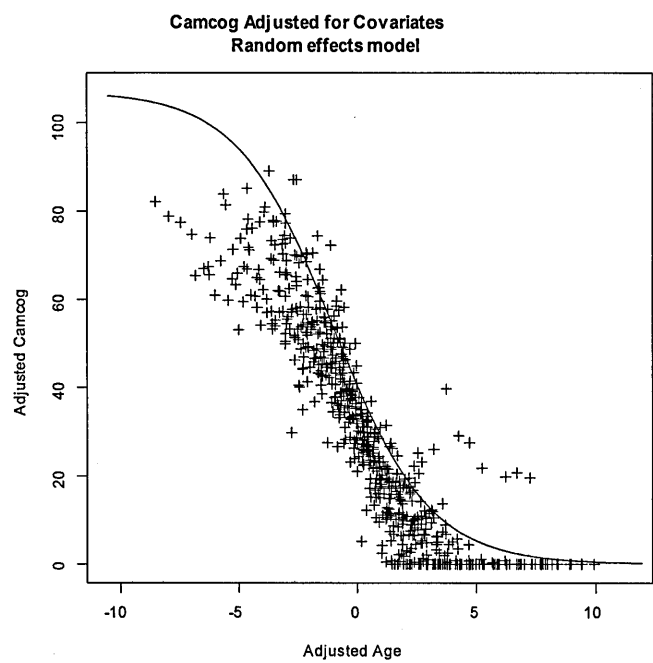


Figure 10.3: Final model and adjusted Camcog points

Chapter 11

Conclusions

I have looked at the Camcog scores over time of a cohort of patients within the Optima project in Oxford. I first modelled the individual patients with a logistic model, and obtained a good fit to the decline of individual patients. However, these patients differ greatly in the age at which they developed the illness, and the time at which they joined the Optima project, which made comparing rates of decline very difficult. By using a linear model in the central part of the decline, I calculated a midpoint age, defined as the age at which the patient would probably have had a Camcog score of 53.5 (half the Camcog fullscale value). I then used values relative to this midpoint age (i.e. plus/minus time from the midpoint) as a timescale, rather than the actual age of the patient. This technique allowed two initially incomparable time scales (age or date) to be reduced to a single scale, and enabled me to amalgamate the data from many patients into a single fixed-effects logistic model. This model was successful, and allowed me to find a few covariates of the many I considered which proved to have a significant effect on the rate of decline.

I then modelled the decline with two random effects logistic models. The random-effects model is more appropriate than the grouped fixed-effects model, as it allows for a random variation from person to person. I then looked for fixed effects within the random variation, using the significant covariates from the grouped fixed-effects model as a guide. I considered the effect of the initial Camcog score being less than full scale; both within the fixed-effects model and the random-effects models, and found that the assumed starting Camcog had little effect on the model.

This model allows a numerical prediction of how the decline rate will vary with differing covariates, and hence from one individual to another. I used the values of the parameters given by the random-effects model to develop a measure, the **impairment ratio**, which allows varying rates of decline to be compared. The larger the impairment ratio, the faster the illness progresses, and the greater the decline in any one year. Of course, because of the nature of the model, the actual numeric value of the points lost in any year depends on the starting Camcog score as well as the impairment ratio. The impairment ratio is very similar to the odds ratio obtained in fitting logistic regressions and has a similar intuitive interpretation.

	h) Estimate for impairment ratio	95% confidence interval for impairment ratio
Use of anticholinesterase drugs	0.66	0.51 to 0.79
midpoint age 40	1.10	1.15 to 1.06
midpoint age 60	0.91	0.87 to 0.94
midpoint age 70	0.81	0.75 to 0.89
midpoint age 80	0.68	0.62 to 0.76
Normal homocysteine not APOE44	0.72	0.62 to 0.83
Normal homocysteine APOE44	1.31	0.61 to 2.18
High homocysteine APOE44	0.64	0.48 to 0.86

Table 11.1: Estimates for impairment ratios

I considered the covariates

- Diagnosis
- APOE genotype;
- Age at midpoint of the illness;
- Age at which symptoms were first noticed;
- Levels of homocysteine in blood at the initial visit;
- Cardiovascular status;
- Gender;
- Age at first visit to Optima;
- Learning correction for first visit - first time the patient has heard the Camdex questionnaire;
- Use of anticholinesterase drugs.

I showed that the use of anticholinesterase drugs APOE genotype, homocysteine and age at midpoint of the illness were significant covariates.

Estimates for impairment ratios and 95% confidence intervals for impairment ratios are shown in Table 11.1. The impairment ratio for a particular covariate is a means of comparing people who differ only in the value of that covariate, but for whom all other factors are equal. If the impairment ratio for a given covariates is < 1, then the covariate is protective, and the lower the impairment ratio, the greater the protection offered. What I mean by a "protective factor" is that over a given time period, a person with the covariate is likely to show a smaller decline that a person without the covariate. If the impairment ratio is > 1, then the covariate is destructive, and a person with the covariate is likely to show a greater decline in cognitive score than someone without the covariate.

As is shown in Table 11.1, people who use anticholinesterase drugs are likely to show a slower decline that people who do not. The illness is likely to progress faster

in younger people, and more slowly in the more elderly, where the age is taken at the midpoint of the illness. For people without the APOE44 allele, an initially normal level of homocysteine is protective, and an initially high level is likely to lead to a faster decline. For carriers of the APOE44 allele, the picture is less clear, but it does seem that a high level of homocysteine may be protective. This unexpected result warrants further investigation as Optima collects more data.

Appendix A

R output of model refinement

```
>
>
> fm1 <- as.formula("dl1 ~AdjAgeAll +
+ DLMid +
+ AdjAgeOnset +
+ AdjAgeEp1 +
+ Gender +
+ DiagasFactor +
+ HcyFactor +
+ FirstEp +
+ DrugsA +
+ DrugsG +
+ APF +
+ CVS +
+ Pulse +
+ Pacemaker +
+ AtrF +
+ DLMid:Gender +
+ Gender:DiagasFactor +
+ HcyFactor:APF")
>
> hblm1 <- glm(fm1,family="binomial",weights=dl2, data=CogDataA)
> summary(hblm1)
Call:
glm(formula = fm1, family = "binomial", data = CogDataA, weights = dl2)
Deviance Residuals:
    Min     1Q   Median     3Q     Max
-10.08552  -1.95328  -0.02396   1.51483  11.82694
Coefficients: (1 not defined because of singularities)
    Estimate Std. Error z value Pr(>|z|)
(Intercept) -0.481935  0.089671  -5.374 7.68e-08 ***
AdjAgeAll   -0.494314  0.005211 -94.857 < 2e-16 ***
```

```

DLMid 0.242659 0.022374 10.846 < 2e-16 ***
AdjAgeOnset 0.010013 0.002574 3.889 0.000100 ***
AdjAgeEp1 0.021986 0.006158 3.570 0.000356 ***
GenderM 0.018020 0.038304 0.470 0.638037
DiagasFactorOD -0.022773 0.023902 -0.953 0.340703
HcyFactorN 0.206217 0.016890 12.209 < 2e-16 ***
FirstEpY 0.153278 0.023426 6.543 6.03e-11 ***
DrugsA1 0.272507 0.028099 9.698 < 2e-16 ***
DrugsG1 0.007161 0.038731 0.185 0.853318
APF 0.221449 0.030248 7.321 2.46e-13 ***
CVSAbnormal -0.208290 0.094590 -2.202 0.027663 *
CVSNormal -0.277682 0.097958 -2.835 0.004587 **
PulseEct 0.297248 0.046263 6.425 1.32e-10 ***
PulseIrr 0.180657 0.050691 3.564 0.000365 ***
PulseNormal 0.287455 0.041591 6.911 4.80e-12 ***
PulseRegirr NA NA NA NA
PacemakerY -0.595757 0.051298 -11.614 < 2e-16 ***
AtrFY 0.305995 0.053748 5.693 1.25e-08 ***
DLMid:GenderM -0.144293 0.032377 -4.457 8.32e-06 ***
GenderM:DiagasFactorOD 0.105695 0.033359 3.168 0.001533 **
HcyFactorN:APF -0.198919 0.049033 -4.057 4.97e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
(Dispersion parameter for binomial family taken to be 1)
Null deviance: 29232.7 on 971 degrees of freedom
Residual deviance: 7689.8 on 950 degrees of freedom
AIC: 11899
Number of Fisher Scoring iterations: 5
> drop1(hblm1,test="Chisq")
Single term deletions

Model:
dl1 ~AdjAgeAll + DLMid + AdjAgeOnset + AdjAgeEp1 + Gender +
  DiagasFactor + HcyFactor + FirstEp + DrugsA + DrugsG + APF +
  CVS + Pulse + Pacemaker + AtrF + DLMid:Gender + Gender:DiagasFactor +

HcyFactor:APF
Df Deviance AIC LRT Pr(Chi)
<none> 7689.8 11898.9
AdjAgeAll 1 19696.9 23904.0 12007.1 < 2.2e-16 ***
AdjAgeOnset 1 7705.1 11912.2 15.3 9.333e-05 ***
AdjAgeEp1 1 7702.6 11909.7 12.7 0.000356 ***
FirstEp 1 7732.8 11940.0 43.0 5.405e-11 ***
DrugsA 1 7783.9 11991.0 94.1 < 2.2e-16 ***

```

```

DrugsG 1 7689.8 11897.0 0.03418 0.853322
CVS 1 7698.9 11906.1 9.1 0.002536 **
Pulse 3 7747.7 11950.9 57.9 1.629e-12 ***
Pacemaker 1 7821.6 12028.7 131.8 < 2.2e-16 ***
AtrF 1 7722.0 11929.2 32.2 1.388e-08 ***
DLMid:Gender 1 7709.7 11916.8 19.9 8.257e-06 ***
Gender:DiagasFactor 1 7699.9 11907.0 10.0 0.001532 **
HcyFactor:APF 1 7706.3 11913.5 16.5 4.859e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
>
> fm1 <- as.formula("dl1 ~AdjAgeAll +
+ DLMid +
+ AdjAgeOnset +
+ AdjAgeEp1 +
+ Gender +
+ DiagasFactor +
+ HcyFactor +
+ FirstEp +
+ DrugsA +
+ APF +
+ CVS +
+ Pulse +
+ Pacemaker +
+ AtrF +
+ DLMid:Gender +
+ Gender:DiagasFactor +
+ HcyFactor:APF")
> hblm1 <- glm(fm1,family="binomial",weights=dl2, data=CogDataA)
> summary(hblm1)
Call:
glm(formula = fm1, family = "binomial", data = CogDataA, weights = dl2)
Deviance Residuals:
    Min     1Q   Median     3Q     Max
-10.08617 -1.95436 -0.02615  1.51398 11.82695
Coefficients: (1 not defined because of singularities)
    Estimate Std. Error z value Pr(>|z|)
(Intercept) -0.481768  0.089667 -5.373 7.75e-08 ***
AdjAgeAll -0.494364  0.005204 -94.989 < 2e-16 ***
DLMid 0.242619  0.022372 10.845 < 2e-16 ***
AdjAgeOnset 0.010007  0.002574  3.887 0.000101 ***
AdjAgeEp1 0.022049  0.006149  3.586 0.000336 ***
GenderM 0.018446  0.038235  0.482 0.629495

```

```

DiagasFactorOD -0.022947 0.023884 -0.961 0.336660
HcyFactorN 0.206453 0.016842 12.259 < 2e-16 ***
FirstEpY 0.153036 0.023389 6.543 6.03e-11 ***
DrugsA1 0.272059 0.027995 9.718 < 2e-16 ***
APF 0.221224 0.030223 7.320 2.49e-13 ***
CVSAbnormal -0.208414 0.094587 -2.203 0.027566 *
CVSNormal -0.277904 0.097950 -2.837 0.004551 **
PulseEct 0.297682 0.046204 6.443 1.17e-10 ***
PulseIrr 0.181362 0.050546 3.588 0.000333 ***
PulseNormal 0.287716 0.041567 6.922 4.46e-12 ***
PulseRegirr NA NA NA NA
PacemakerY -0.595805 0.051298 -11.615 < 2e-16 ***
AtrFY 0.305438 0.053664 5.692 1.26e-08 ***
DLMid:GenderM -0.144558 0.032345 -4.469 7.85e-06 ***
GenderM:DiagasFactorOD 0.105802 0.033354 3.172 0.001513 **
HcyFactorN:APF -0.198499 0.048981 -4.053 5.06e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
(Dispersion parameter for binomial family taken to be 1)
Null deviance: 29232.7 on 971 degrees of freedom
Residual deviance: 7689.8 on 951 degrees of freedom
AIC: 11897
Number of Fisher Scoring iterations: 5
> drop1(hblm1,test="Chisq")
Single term deletions

Model:
dl1 ~AdjAgeAll + DLMid + AdjAgeOnset + AdjAgeEp1 + Gender +
  DiagasFactor + HcyFactor + FirstEp + DrugsA + APF + CVS +
  Pulse + Pacemaker + AtrF + DLMid:Gender + Gender:DiagasFactor +
  HcyFactor:APF
Df Deviance AIC LRT Pr(Chi)
<none> 7689.8 11897.0
AdjAgeAll 1 19730.6 23935.7 12040.7 < 2.2e-16 ***
AdjAgeOnset 1 7705.1 11910.2 15.2 9.422e-05 ***
AdjAgeEp1 1 7702.7 11907.8 12.9 0.0003355 ***
FirstEp 1 7732.9 11938.0 43.0 5.410e-11 ***
DrugsA 1 7784.3 11989.4 94.5 < 2.2e-16 ***
CVS 1 7699.0 11904.1 9.1 0.0024937 **
Pulse 3 7747.8 11948.9 58.0 1.605e-12 ***
Pacemaker 1 7821.7 12026.8 131.8 < 2.2e-16 ***
AtrF 1 7722.0 11927.2 32.2 1.400e-08 ***
DLMid:Gender 1 7709.8 11915.0 20.0 7.785e-06 ***
Gender:DiagasFactor 1 7699.9 11905.0 10.1 0.0015125 **

```

```

HcyFactor:APF 1 7706.3 11911.5 16.5 4.948e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
>
> fm1 <- as.formula("dl1 ~AdjAgeAll +
+ DLMid +
+ AdjAgeOnset +
+ AdjAgeEp1 +
+ Gender +
+ DiagasFactor +
+ HcyFactor +
+ FirstEp +
+ DrugsA +
+ APF +
+ CVS +
+ Pulse +
+ DLMid:Gender +
+ Gender:DiagasFactor +
+ HcyFactor:APF")
> hblm1 <- glm(fm1,family="binomial",weights=dl2, data=CogDataA)
> summary(hblm1)
Call:
glm(formula = fm1, family = "binomial", data = CogDataA, weights = dl2)
Deviance Residuals:
    Min 1Q Median 3Q Max
-9.997438 -1.971252  0.003977  1.504654 11.842202
Coefficients: (1 not defined because of singularities)
      Estimate Std. Error z value Pr(>|z|)
(Intercept) -0.429083  0.089266  -4.807 1.53e-06 ***
AdjAgeAll -0.490860  0.005189 -94.600 < 2e-16 ***
DLMid 0.191879  0.021933  8.749 < 2e-16 ***
AdjAgeOnset 0.007373  0.002523  2.922 0.003478 **
AdjAgeEp1 0.030657  0.006058  5.061 4.17e-07 ***
GenderM -0.050763  0.037491 -1.354 0.175728
DiagasFactorOD -0.052000  0.023776 -2.187 0.028738 *
HcyFactorN 0.218032  0.016726 13.036 < 2e-16 ***
FirstEpY 0.155690  0.023364  6.664 2.67e-11 ***
DrugsA1 0.270230  0.027907  9.683 < 2e-16 ***
APF 0.237667  0.030103  7.895 2.90e-15 ***
CVSAbnormal -0.177316  0.094197 -1.882 0.059782 .
CVSNormal -0.232284  0.097546 -2.381 0.017253 *
PulseEct 0.268310  0.045860  5.851 4.90e-09 ***
PulseIrr 0.164646  0.049792  3.307 0.000944 ***

```

```

PulseNormal 0.247527 0.041228 6.004 1.93e-09 ***
PulseRegirr NA NA NA NA
DLMid:GenderM -0.075545 0.031408 -2.405 0.016158 *
GenderM:DiagasFactorOD 0.112397 0.032544 3.454 0.000553 ***
HcyFactorN:APF -0.231676 0.048754 -4.752 2.01e-06 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
(Dispersion parameter for binomial family taken to be 1)

Null deviance: 29232.7 on 971 degrees of freedom
Residual deviance: 7821.7 on 953 degrees of freedom
AIC: 12025
Number of Fisher Scoring iterations: 5
> drop1(hblm1,test="Chisq")
Single term deletions

Model:
dl1 ~AdjAgeAll + DLMid + AdjAgeOnset + AdjAgeEp1 + Gender +
  DiagasFactor + HcyFactor + FirstEp + DrugsA + APF + CVS +
  Pulse + DLMid:Gender + Gender:DiagasFactor + HcyFactor:APF
Df Deviance AIC LRT Pr(Chi)
<none> 7821.7 12024.8
AdjAgeAll 1 19749.5 23950.6 11927.8 < 2.2e-16 ***
AdjAgeOnset 1 7830.3 12031.4 8.6 0.0033753 **
AdjAgeEp1 1 7847.3 12048.4 25.6 4.141e-07 ***
FirstEp 1 7866.3 12067.4 44.6 2.380e-11 ***
DrugsA 1 7915.5 12116.6 93.8 < 2.2e-16 ***
CVS 1 7827.5 12028.6 5.8 0.0162118 *
Pulse 3 7865.8 12063.0 44.2 1.394e-09 ***
DLMid:Gender 1 7827.5 12028.6 5.8 0.0161450 *
Gender:DiagasFactor 1 7833.6 12034.7 11.9 0.0005523 ***
HcyFactor:APF 1 7844.3 12045.5 22.7 1.940e-06 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
>
> fm1 <- as.formula("dl1 ~AdjAgeAll +
+ DLMid +
+ AdjAgeOnset +
+ AdjAgeEp1 +
+ Gender +
+ HcyFactor +
+ FirstEp +
+ DrugsA +
+ APF +
+ CVS +

```

```

+ Pulse +
+ DLMid:Gender +
+ HcyFactor:APF")
>
> hblm1 <- glm(fm1,family="binomial",weights=dl2, data=CogDataA)
> summary(hblm1)
Call:
glm(formula = fm1, family = "binomial", data = CogDataA, weights = dl2)
Deviance Residuals:
    Min 1Q Median 3Q Max
-10.08604 -1.99427  0.00734  1.54829 11.92821
Coefficients:  (1 not defined because of singularities)
    Estimate Std. Error z value Pr(>|z|)
(Intercept) -0.418508  0.089212 -4.691 2.72e-06 ***
AdjAgeAll -0.492130  0.005176 -95.071 < 2e-16 ***
DLMid 0.187797  0.021823  8.605 < 2e-16 ***
AdjAgeOnset 0.007761  0.002517  3.083 0.002049 **
AdjAgeEp1 0.033239  0.006003  5.537 3.08e-08 ***
GenderM -0.012067  0.035719 -0.338 0.735501
HcyFactorN 0.216998  0.016702 12.992 < 2e-16 ***
FirstEpY 0.155625  0.023364  6.661 2.72e-11 ***
DrugsA1 0.268039  0.027669  9.687 < 2e-16 ***
APF 0.238956  0.029485  8.104 5.31e-16 ***
CVSAbnormal -0.206685  0.093570 -2.209 0.027184 *
CVSNormal -0.281347  0.095500 -2.946 0.003219 **
PulseEct 0.285363  0.045656  6.250 4.10e-10 ***
PulseIrr 0.183614  0.049334  3.722 0.000198 ***
PulseNormal 0.265439  0.040945  6.483 9.00e-11 ***
PulseRegirr NA NA NA NA
DLMid:GenderM -0.080926  0.031248 -2.590 0.009604 **
HcyFactorN:APF -0.235171  0.048754 -4.824 1.41e-06 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
(Dispersion parameter for binomial family taken to be 1)
Null deviance: 29232.7 on 971 degrees of freedom
Residual deviance: 7833.7 on 955 degrees of freedom
AIC: 12033
Number of Fisher Scoring iterations: 5
> drop1(hblm1,test="Chisq")
Single term deletions

Model:
dl1 ~ AdjAgeAll + DLMid + AdjAgeOnset + AdjAgeEp1 + Gender +
    HcyFactor + FirstEp + DrugsA + APF + CVS + Pulse + DLMid:Gender +

```



```

HcyFactor:APF
Df Deviance AIC LRT Pr(Chi)
<none> 7833.7 12032.8
AdjAgeAll 1 19894.4 24091.5 12060.7 < 2.2e-16 ***
AdjAgeOnset 1 7843.3 12040.4 9.6 0.0019798 **
AdjAgeEp1 1 7864.4 12061.5 30.7 3.058e-08 ***
FirstEp 1 7878.3 12075.4 44.6 2.427e-11 ***
DrugsA 1 7927.5 12124.7 93.8 < 2.2e-16 ***
CVS 1 7846.3 12043.4 12.6 0.0003868 ***
Pulse 3 7883.4 12076.5 49.7 9.121e-11 ***
DLMid:Gender 1 7840.4 12037.5 6.7 0.0095955 **
HcyFactor:APF 1 7857.0 12054.2 23.3 1.357e-06 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
>
> CogDataA$PulseIrr <- CogDataA$Pulse
> CogDataA$PulseIrr <- 0
> CogDataA$PulseIrr[CogDataA$Pulse == "Irr"] <- 1
> summary(CogDataA$PulseIrr)
  Min. 1st Qu.  Median Mean 3rd Qu.  Max.
0.00000 0.00000 0.00000 0.06687 0.00000 1.00000
> CogDataA$PulseIrr <- as.factor(CogDataA$PulseIrr)
> summary(CogDataA$PulseIrr)
 0 1
907 65
>
> fm1 <- as.formula("dl1 ~AdjAgeAll +
+ DLMid +
+ AdjAgeOnset +
+ AdjAgeEp1 +
+ Gender +
+ HcyFactor +
+ FirstEp +
+ DrugsA +
+ APF +
+ CVS +
+ PulseIrr +
+ DLMid:Gender +
+ HcyFactor:APF")
>
> hblm1 <- glm(fm1,family="binomial",weights=dl2, data=CogDataA)
> summary(hblm1)
Call:

```

```

glm(formula = fm1, family = "binomial", data = CogDataA, weights = dl2)
Deviance Residuals:
    Min      1Q  Median      3Q     Max
-10.01190 -1.95014  0.03448  1.52149 11.98922

Coefficients:
    Estimate Std. Error z value Pr(>|z|)
(Intercept) -0.397521  0.089077 -4.463 8.09e-06 ***
AdjAgeAll   -0.490902  0.005171 -94.939 < 2e-16 ***
DLMid       0.162138  0.021465  7.554 4.23e-14 ***
AdjAgeOnset  0.006170  0.002473  2.495 0.0126 *
AdjAgeEp1   0.032907  0.005848  5.627 1.83e-08 ***
GenderM     -0.023606  0.035608 -0.663 0.5074
HcyFactorN  0.206372  0.016602 12.430 < 2e-16 ***
FirstEpY    0.161732  0.023344  6.928 4.26e-12 ***
DrugsA1     0.278196  0.027480 10.123 < 2e-16 ***
APF         0.241033  0.029205  8.253 < 2e-16 ***
CVSAbnormal  0.046609  0.085185  0.547 0.5843
CVSNormal   -0.015214  0.086520 -0.176 0.8604
PulseIrr1   -0.071489  0.030374 -2.354 0.0186 *
DLMid:GenderM -0.063419  0.031062 -2.042 0.0412 *
HcyFactorN:APF -0.222183  0.048689 -4.563 5.04e-06 ***

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
(Dispersion parameter for binomial family taken to be 1)

Null deviance: 29232.7 on 971 degrees of freedom
Residual deviance: 7877.9 on 957 degrees of freedom
AIC: 12073
Number of Fisher Scoring iterations: 5
> drop1(hblm1,test="Chisq")
Single term deletions

Model:
dl1 ~ AdjAgeAll + DLMid + AdjAgeOnset + AdjAgeEp1 + Gender +
    HcyFactor + FirstEp + DrugsA + APF + CVS + PulseIrr + DLMid:Gender +

HcyFactor:APF
Df Deviance AIC LRT Pr(Chi)
<none> 7877.9 12073.0
AdjAgeAll 1 19908.9 24102.1 12031.1 < 2.2e-16 ***
AdjAgeOnset 1 7884.1 12077.3 6.3 0.01236 *
AdjAgeEp1 1 7909.5 12102.7 31.7 1.829e-08 ***
FirstEp 1 7926.1 12119.3 48.3 3.749e-12 ***
DrugsA 1 7980.4 12173.5 102.5 < 2.2e-16 ***
CVS 2 7886.8 12077.9 8.9 0.01171 *

```

```

PulseIrr 1 7883.4 12076.5 5.5 0.01852 *
DLMid:Gender 1 7882.0 12075.2 4.2 0.04117 *
HcyFactor:APF 1 7898.8 12091.9 20.9 4.871e-06 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
>
> fm1 <- as.formula("dl1 ~AdjAgeAll +
+ DLMid +
+ AdjAgeOnset +
+ AdjAgeEp1 +
+ Gender +
+ HcyFactor +
+ FirstEp +
+ DrugsA +
+ APF +
+ PulseIrr +
+ DLMid:Gender +
+ HcyFactor:APF")
>
> hblm1 <- glm(fm1,family="binomial",weights=dl2, data=CogDataA)
> summary(hblm1)
Call:
glm(formula = fm1, family = "binomial", data = CogDataA, weights = dl2)
Deviance Residuals:
    Min 1Q Median 3Q Max
-10.1829 -1.9654  0.0735  1.5450 11.9937
Coefficients:
    Estimate Std. Error z value Pr(>|z|)
(Intercept) -0.377140  0.030976 -12.175 < 2e-16 ***
AdjAgeAll -0.490227  0.005164 -94.928 < 2e-16 ***
DLMid 0.166962  0.021401  7.802 6.11e-15 ***
AdjAgeOnset 0.005982  0.002467  2.425 0.0153 *
AdjAgeEp1 0.029769  0.005748  5.179 2.23e-07 ***
GenderM -0.021337  0.035603 -0.599 0.5490
HcyFactorN 0.207330  0.016584 12.502 < 2e-16 ***
FirstEpY 0.161578  0.023328  6.926 4.32e-12 ***
DrugsA1 0.277394  0.027448 10.106 < 2e-16 ***
APF 0.241938  0.029190  8.288 < 2e-16 ***
PulseIrr1 -0.061466  0.030194 -2.036 0.0418 *
DLMid:GenderM -0.060730  0.031058 -1.955 0.0505 .
HcyFactorN:APF -0.213965  0.048627 -4.400 1.08e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

(Dispersion parameter for binomial family taken to be 1)
Null deviance: 29232.7 on 971 degrees of freedom
Residual deviance: 7886.8 on 959 degrees of freedom
AIC: 12078
Number of Fisher Scoring iterations: 5
> drop1(hblm1,test="Chisq")
Single term deletions

Model:
dl1 ~AdjAgeAll + DLMid + AdjAgeOnset + AdjAgeEp1 + Gender +
HcyFactor + FirstEp + DrugsA + APF + PulseIrr + DLMid:Gender +
HcyFactor:APF
Df Deviance AIC LRT Pr(Chi)
<none> 7886.8 12077.9
AdjAgeAll 1 19923.1 24112.2 12036.3 < 2.2e-16 ***
AdjAgeOnset 1 7892.7 12081.8 5.9 0.01509 *
AdjAgeEp1 1 7913.6 12102.7 26.8 2.240e-07 ***
FirstEp 1 7935.0 12124.1 48.2 3.797e-12 ***
DrugsA 1 7988.9 12178.0 102.1 < 2.2e-16 ***
PulseIrr 1 7890.9 12080.0 4.1 0.04167 *
DLMid:Gender 1 7890.6 12079.7 3.8 0.05051 .
HcyFactor:APF 1 7906.2 12095.3 19.4 1.049e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
>
> fm1 <- as.formula("dl1 ~AdjAgeAll +
+ DLMid +
+ AdjAgeOnset +
+ AdjAgeEp1 +
+ HcyFactor +
+ FirstEp +
+ DrugsA +
+ APF +
+ PulseIrr +
+ HcyFactor:APF")
>
> hblm1 <- glm(fm1,family="binomial",weights=dl2, data=CogDataA)
> summary(hblm1)
Call:
glm(formula = fm1, family = "binomial", data = CogDataA, weights = dl2)
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-9.99911 -1.92543  0.05288  1.49966 12.09952

Coefficients:

```

```

Estimate Std. Error z value Pr(>|z|)
(Intercept) -0.391555 0.026994 -14.506 < 2e-16 ***
AdjAgeAll -0.488503 0.005162 -94.629 < 2e-16 ***
DLMid 0.143980 0.015872 9.071 < 2e-16 ***
AdjAgeOnset 0.004712 0.002456 1.918 0.05510 .
AdjAgeEp1 0.030037 0.005718 5.253 1.49e-07 ***
HcyFactorN 0.201162 0.016358 12.297 < 2e-16 ***
FirstEpY 0.159373 0.023315 6.836 8.16e-12 ***
DrugsA1 0.254600 0.027183 9.366 < 2e-16 ***
APF 0.244121 0.029118 8.384 < 2e-16 ***
PulseIrr1 -0.090490 0.029681 -3.049 0.00230 **
HcyFactorN:APF -0.223752 0.048043 -4.657 3.20e-06 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
(Dispersion parameter for binomial family taken to be 1)
Null deviance: 29232.7 on 971 degrees of freedom
Residual deviance: 7924.3 on 961 degrees of freedom
AIC: 12111
Number of Fisher Scoring iterations: 5
> drop1(hblm1,test="Chisq")
Single term deletions

Model:
dl1 ~AdjAgeAll + DLMid + AdjAgeOnset + AdjAgeEp1 + HcyFactor +
  FirstEp + DrugsA + APF + PulseIrr + HcyFactor:APF
Df Deviance AIC LRT Pr(Chi)
<none> 7924.3 12111.5
AdjAgeAll 1 19956.0 24141.1 12031.6 < 2.2e-16 ***
DLMid 1 8006.8 12191.9 82.5 < 2.2e-16 ***
AdjAgeOnset 1 7928.0 12113.2 3.7 0.054662 .
AdjAgeEp1 1 7951.9 12137.1 27.6 1.500e-07 ***
FirstEp 1 7971.3 12156.4 47.0 7.216e-12 ***
DrugsA 1 8012.1 12197.2 87.7 < 2.2e-16 ***
PulseIrr 1 7933.7 12118.8 9.3 0.002276 **
HcyFactor:APF 1 7946.1 12131.2 21.8 3.088e-06 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
>
> fm1 <- as.formula("dl1 ~AdjAgeAll +
+ DLMid +
+ AdjAgeEp1 +
+ HcyFactor +
+ FirstEp +
+ DrugsA +

```

```

+ APF +
+ PulseIrr +
+ HcyFactor:APF")
>
> hblm1 <- glm(fm1,family="binomial",weights=dl2, data=CogDataA)
> summary(hblm1)
Call:
glm(formula = fm1, family = "binomial", data = CogDataA, weights = dl2)
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-9.95032 -1.92435  0.05608  1.47875 12.06670

Coefficients:
    Estimate Std. Error z value Pr(>|z|)
(Intercept) -0.407189   0.025737 -15.821 < 2e-16 ***
AdjAgeAll -0.489412   0.005139 -95.227 < 2e-16 ***
DLMid 0.144643   0.015870   9.114 < 2e-16 ***
AdjAgeEp1 0.035106   0.005069   6.926 4.34e-12 ***
HcyFactorN 0.201455   0.016356 12.317 < 2e-16 ***
FirstEpY 0.158337   0.023308   6.793 1.10e-11 ***
DrugsA1 0.256501   0.027176   9.438 < 2e-16 ***
APF 0.247926   0.029047   8.535 < 2e-16 ***
PulseIrr1 -0.090491   0.029677  -3.049 0.00229 **
HcyFactorN:APF -0.221809 0.048040  -4.617 3.89e-06 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
(Dispersion parameter for binomial family taken to be 1)

Null deviance: 29233 on 971 degrees of freedom
Residual deviance: 7928 on 962 degrees of freedom
AIC: 12113
Number of Fisher Scoring iterations: 5
> drop1(hblm1,test="Chisq")
Single term deletions

Model:
dl1 ~AdjAgeAll + DLMid + AdjAgeEp1 + HcyFactor + FirstEp + DrugsA +
    APF + PulseIrr + HcyFactor:APF
    Df Deviance AIC LRT Pr(Chi)
<none> 7928.0 12113.2
AdjAgeAll 1 20217.4 24400.5 12289.4 < 2.2e-16 ***
DLMid 1 8011.3 12194.4 83.2 < 2.2e-16 ***
AdjAgeEp1 1 7976.1 12159.3 48.1 4.056e-12 ***
FirstEp 1 7974.4 12157.5 46.4 9.719e-12 ***
DrugsA 1 8017.1 12200.2 89.1 < 2.2e-16 ***
PulseIrr 1 7937.3 12120.5 9.3 0.002273 **

```

```
HcyFactor:APF 1 7949.4 12132.6 21.4 3.753e-06 ***
```

```
---
```

```
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
>
```

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